REMARKS

Applicant's representative appreciates the Examiner extending the courtesy of a personal interview on May 11, 2006. Applicant's representative agrees with the Examiner's Interview Summary mailed May 19, 2006.

Claims 1 and 22 are amended. Claims 20, 21, 24 and 30 are cancelled. Claims 1, 4, 7-11, 13 and 20-29 stand rejected. Claim 31 is added. By this amendment, Claims 1, 4, 7-11, 13, 22, 23, and 25-29 and 31 are pending.

Claim Rejections under 35 U.S.C. § 102(a)

Claims 1, 4, 7, 13, 20-22, 28-30 are rejected under 35 U.S.C. §102(a) as being anticipated by Bisson (FR 2785811, published May 19, 2000, hereinafter *Bisson*). Claims 8-11 and 23-27 are not rejected.

Claim 1 has been amended to recite biocompatible micronized high density polyethylene particles having a size greater than one-hundred microns. Support for this amendment is found in the specification on page 4, paragraph 49. *Bisson's* particles are less than one-hundred microns. On page 2, next to the last paragraph, *Bisson* discloses particle diameters of more than approximately 10 microns, in particular 30-100 microns, preferably 30-60 microns. Applicant also wishes to point out that the translation of page 2, line 12 of the French version of Bisson, "entre 30 et 100" should be between 30 and 100 and not 30-100, since the French word "entre" means "between". *Bisson* teaches away from using particles with diameters greater than 100 microns (see the French version of *Bisson* page 2, line 19, and the English version of *Bisson* page 3 second paragraph) which recites the disadvantages of using particles with diameters more than 100 microns as they risk giving the tissue a "visually perceivable roughness"). {Applicant submits both the French and English versions of *Bisson* as Exhibit A for the Examiner's convenience}. Applicant wishes to point out that this 100 microns (see the French version of *Bisson* page 2, line 19)

was incorrectly translated in the English version as 1000 microns (page 3, second paragraph). *Bisson* further teaches away from using particles with diameters more than 100 microns in this paragraph by stating that it would be more difficult to inject the product through a needle. Applicant respectfully asserts that amended Claim 1 is novel over *Bisson* and requests withdrawal of the rejection of Claim 1 and its dependent claims.

Claim 22 has been amended to include limitations found in Claim 24, namely the K values of polyvinylpyrrolidone. Claim 24 was not rejected in view of *Bisson*. Accordingly, amended Claim 22 is novel over *Bisson* and Applicant requests withdrawal of the rejection of Claim 22 and its dependent claims.

Claim rejections under 35 U.S.C. §112, first paragraph

Claims 1, 4, 7-11, 13 and 20-30 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. This is a new matter rejection. Claims 20, 21, 24 and 30 are cancelled, rendering moot their rejection. Applicant traverses and asserts that he was in possession of the claimed invention at the time the application was filed for at least the following reasons.

The specification discloses solid polymer particles as biocompatible (micronized) polyethylene particles made from MEDPOR in paragraphs 0030, 0043 and 0058 and in the Abstract. The polyethylene in MEDPOR is high density polyethylene (HDPE), as declared by the Applicant previously (January, 2006) and as known to one of ordinary skill in the art. The Declarations of Applicant and Dr. Perkins filed in January, 2006, both describe Applicant's disclosure of his claimed invention in December of 1999, comprising high density polyethylene particles in a carrier for use in soft tissue augmentation.

One of ordinary skill in the art referred to MEDPOR as high density polyethylene before and after the filing of this patent application. Applicant submits

three articles attached as Exhibits B, C, and D which demonstrate this fact. In Exhibit B (Lacey et al., The Journal of Craniofacial Surgery, vol. 4, pp 74-78, 1993), Lacey mentions on page 74, second column, third paragraph, that porous high density polyethylene (MEDPOR) provides the standard of biocompatibility. In Exhibit C (Williams et al., Arch. Otolaryngol. Head & Neck Surgery, vol. 123, pp. 578-583, 1997) Williams discloses porous high density polyethylene (MEDPOR) implants (see Objective, pp 578). In Exhibit D (Lee et al., Arch Otolaryngol. Head & Neck Surgery, vol. 131, pp. 578-583, 2005), Lee describes use of porous high density polyethylene (MEDPOR) on page 446, column 2, and in the figure legends. Accordingly, one of skill in the art knows and knew before the application was filed that MEDPOR is high density polyethylene. Please see the concurrently filed Declaration of Dr. Robert D. Wallace as one of ordinary skill in the art attesting that the term MEDPOR was and is used to indicate high density polyethylene and that the terms MEDPOR and high density polyethylene have been used interchangeably.

Therefore, by reciting "MEDPOR (biocompatible (micronized) polyethylene)", Applicant was de facto referring to HDPE. Applicant was in possession of his claimed invention comprising biocompatible micronized high density polyethylene particles when he referred to MEDPOR (biocompatible (micronized) polyethylene) in the patent application. Further, Applicant was in possession of his claimed invention comprising biocompatible micronized high density polyethylene particles when he disclosed this invention to Dr. Perkins in December of 1999.

The Examiner implies that HDPE is a chemical genus composed of various species and seems to assert that Applicant is trying to claim a genus. The Examiner notes that HDPE is produced in many forms, most of which are not suitable for surgery, and mentions various forms that are used in Tupperware, milk cartons, plastic bags, etc. Applicant responds that MEDPOR Biomaterial (whether in the porous or non-porous form), Tupperware, milk cartons or any other forms of HDPE products are not different species of the genus "high-density" polyethylene. These

items are all made of the same material, HDPE, but they are processed differently. Therefore, Tupperware, milk cartons, MEDPOR, etc. are not different forms of HDPE. Instead, HDPE is processed differently to create different products. The grade of HDPE, which is used to make implantable MEDPOR implants, is currently used across the plastics industry to make a wide range of products outside the medical field. High-density polyethylene is synthesized as flakes or powder. This powder is then processed to various extents based on the final application (e.g., containers or MEDPOR implants). Based on the final application, HDPE will be subjected to various manufacturing processes such as injection molding, blow molding, compression molding, sintering, etc. If the HDPE-containing article is intended to be implanted, it will be made in an anatomical shape and sterilized. If the HDPE-containing article is intended to be used as a container, it will be made in a suitable shape and will not be sterilized.

The Examiner asserted that "...high density polyethylene is produced in many forms, most of which are not suitable for surgery...". Applicant responds that the HDPE used to make consumer products can and is indeed used to make implants suitable for surgery. It is the chemical structure, not the process, which renders HDPE biocompatible.

The Ho, T. "Biopolymers in Otolaryngology" Baylor College of Medicine reference used by the examiner that states "...only "porous" high-density polyethylene is used in surgery because it allows "soft tissue ingrowth"..." is not accurate as non-porous forms of HDPE are used in surgery (see MEDPOR BARRIER implants from Porex Surgical Group). This further proves that the chemical structure of implants, not their process of manufacture, confers biocompatibility.

The Examiner implies that HDPE is a chemical genus composed of various species and seems to assert that Applicant is trying to claim a genus. The analogy used is halogens (the genus) being composed of species (F, Cl, Br, etc.). According to the examiner, MEDPOR, Tupperware, milk cartons, etc., are species of the genus HDPE. Applicant respectfully traverses for the following reasons. F, Cl, Br, all have

different chemical structures and are different species that belong to a chemical group (or genus) called halogens. Applicant asserts that HDPE is a species within the genus of polyethylene. Other species within the genus of polyethylene include low density polyethylene, linear low density polyethylene and ultra high molecular weight polyethylene. MEDPOR, Tupperware, and milk cartons made of HDPE all have the same chemical structure. What differentiates these products is the way they are processed, not their chemical structures. Therefore, these products are not different species within a chemical genus. The same grade of HDPE can be (and is) used to make consumer products as well as implants. HDPE is the starting material to make these different objects, these objects are not different types of HDPE.

Accordingly, Applicant's invention, as claimed, was in Applicant's possession at the time of filing the application and the claims do not recite a genus. Accordingly, in view of these remarks and identified support in the specification, Applicant respectfully asserts that the rejection of Claims 1, 4, 7-11, 13 and 20-30 under 35 U.S.C. §112, first paragraph, has been overcome and requests its withdrawal.

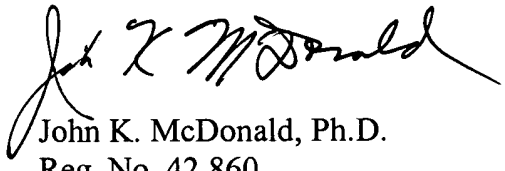
CONCLUSION

Based upon the amendments and remarks provided above, Applicant believes the pending Claims are in condition for allowance. A Notice of Allowance is therefore respectfully solicited.

This request for continued examination and response is considered timely filed and fully responsive to the Final Office Action of April 27, 2006 in view of the accompanying petition for a one month extension of time. A Form PTO-2038 for the amount of $910.00 is enclosed ($790.00 for RCE fee for large entity under 37 CFR §1.17(e) and $120.00 for one-month extension of time fee for large entity under 37 CFR §1.17(a)(1)); however, the Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes any informalities remain in the application that may be corrected by Examiner's Amendment, or there are any other issues that can be resolved by telephone interview, a telephone call to the undersigned attorney at (404) 745-2470 is respectfully solicited.

Respectfully submitted,



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(54) COMPOSITION COMPRENANT DES MICROPARTICULES POREUSES ET UN AGENT DE SUSPENSION ET SON UTILISATION EN TANT QU'IMPLANT.

(57) L'invention concerne une composition comprenant:
- des microparticules poreuses dont le diamètre des pores exclut la pénétration d'éléments figurés ayant un poids moléculaire supérieur à 1000 kilodaltons, et
- un agent de suspension biocompatible,
ainsi que son utilisation pour la fabrication d'un implant hétérologue histocompatible.

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EXHIBIT A

La présente invention concerne des compositions comprenant des microparticules poreuses et/ou un agent de suspension, tous deux biocompatibles tant au niveau cellulaire que tissulaire ou général, utilisables pour une implantation dans un tissu pour, en particulier, augmenter le volume de ce tissu (« *soft tissue augmentation* »), en vue notamment de corriger de manière durable un déficit d'aspect ou de fonctionnalité de ce tissu ou organe.

L'invention s'adresse tout particulièrement à la chirurgie plastique et esthétique, à la chirurgie reconstructrice, à la chirurgie urologique, etc...

L'utilisation d'implants pour la correction ou l'atténuation de lésions d'origine organique ou traumatique a connu une accélération rapide et continue depuis le début des années 80. Les matériaux de référence restent le collagène et les dérivés de silicone. D'autres polymères naturels, tels que par exemple l'acide hyaluronique, ou synthétiques prennent une importance croissante.

L'utilisation de dérivés d'origine animale rencontre de plus en plus de résistance, d'abord d'ordre psychologique, ensuite parce que la persistance de leur effet est limitée dans le temps.

De plus, il est connu que les composés d'origine animale, tels que le collagène bovin, sont à l'origine de réactions allergiques dans environ 3 % des cas. La fréquence et la gravité de ces réactions se trouvent aggravées par la nécessité de procéder à des injections répétées nécessaires au maintien d'un résultat satisfaisant. Les dérivés de silicone et d'huile de silicone, bien qu'interdits dans certains pays, restent parmi les plus utilisés pour obtenir un effet durable. Leur utilisation est cependant souvent associée à des problèmes locaux (siliconomes) ou de migration à des distances parfois considérables du site de leur implantation.

Une autre technique connue de comblement consiste à injecter des microsphères de matériaux divers (plastique, verre, céramique, ...) dans les tissus. Ces particules sont en général d'une taille supérieure à la limite d'absorption (phagocytose) par les monocytes, qui vont constituer une pellicule fibreuse à leur surface afin de les isoler des tissus environnants. De telles particules sont décrites par exemple dans le brevet US 5,344,452.

Le résultat de ces injections est généralement durable, mais il est connu que les particules peuvent migrer à distance de leur site d'implantation avec, comme complication, un risque d'obstruction des structures microvasculaires, pouvant entraîner une ischémie ou embolie.

On a maintenant trouvé qu'en utilisant des microparticules ayant une porosité contrôlée et/ou un agent de suspension, par exemple, sous forme de gel, on

pouvait obtenir une pénétration par des fibrilles protéiques et/ou glycaniques des tissus implantés permettant un ancrage matriciel micro-fibrillaire limitant significativement les risques de migration à distance du site d'implantation.

L'invention a donc pour objet une composition comprenant :

- des microparticules poreuses dont le diamètre des pores exclut la pénétration d'éléments figurés ayant un poids moléculaire supérieur à 1000 kilodaltons, et
- un agent de suspension biocompatible.

La composante solide de la composition selon l'invention est constituée de microparticules poreuses biocompatibles.

Les microparticules utilisées dans la composition selon l'invention auront de préférence une forme sphérique ou ovoïde, d'un diamètre supérieur à environ 10 μm, en particulier compris entre 30 et 100 μm, de préférence entre 30 et 60 μm.

Lorsque les microparticules ne sont pas sphériques, on entend par « diamètre » le plus grand diamètre de la surface ayant la plus petite section transversale.

Les particules de taille inférieure à 10 μm seraient facilement entraînées, activement ou passivement, à distance de leur site d'implantation.

Inversement, l'utilisation de particules d'une taille supérieure à environ 100 μm risquerait de donner aux tissus une rugosité perceptible visuellement ou au toucher dans le cas d'une implantation superficielle. De plus, le produit serait plus difficilement injecté au travers d'une aiguille de petit diamètre, 30G par exemple, nécessaire à une procédure atraumatique.

Une caractéristique avantageuse des microparticules utilisables selon l'invention est qu'elles présentent une structure imparfaitement rigide, permettant une légère déformation en cas de compression. Par « structure imparfaitement rigide », on entend une structure telle que sous l'effet d'une compression axiale d'une valeur maximale compatible avec la résistance du tissu vivant environnant (inférieure ou égale à environ 3 kg/cm^2), les particules ne se briseront pas et leur taux de déformation selon cet axe sera compris entre 0 % et 40 %. Cette déformation limitera la tendance au déplacement des particules, phénomène connu dans le cas de particules rigides sous l'appellation « effet graine de melon » (« melon pip effect »), qui est d'autant plus accentué que la surface des microparticules est lisse et lubrifiée.

Les microparticules utilisables selon l'invention, qui peuvent constituer l'essentiel de la composition, présentent une structure poreuse. Le diamètre des pores est déterminé de façon à exclure la pénétration des particules par des éléments figurés de taille supérieure à 1 000 kilodaltons. On recherchera une porosité telle qu'elle

favorisera la pénétration de macromolécules de structure naturellement présentes dans les tissus environnant l'implant. Ces macromolécules, en particulier d'élastine, de collagène ou de glycosaminoglycanes (GAGs), de nature microfibrillaire, forment un réseau intriqué qui relie les microparticules qu'elles pénètrent.

En particulier, les microparticules ont des pores dont le diamètre exclut la pénétration d'éléments figurés ayant un poids moléculaire compris entre 0,5 kilodalton et 5 000 kilodaltons, de préférence entre 1 kilodalton et 1 000 kilodaltons.

Le système d'ancrage ainsi obtenu forme une structure souple et élastique dont la cohérence s'accentue dans le temps au fur et à mesure qu'un nombre croissant de liens microfibrillaires en assure la réticulation. La solidité et la consistance des structures ainsi obtenues ressemblent à celles de la matrice extracellulaire, assurant un confort et un aspect optimal.

Cette consistance souple et déformable des éléments comme de l'ensemble, assure un risque minimum de traumatisme, générateur de lésions et d'infection, des tissus.

De préférence, les microparticules sont présentes dans la composition à raison d'environ 0,1 % à 75 % en poids, de préférence de 10 % à 40 %, les pourcentages étant exprimés par rapport au poids total de la composition.

Le matériau constituant les microparticules sera cyto- et hystocompatible, et plus généralement biocompatible au sens de la Norme ISO EN 10993. Il sera de préférence un polymère, dont les monomères de départ ne présentent pas de caractère de toxicité incompatible avec l'utilisation envisagée.

On utilisera par exemple un polymère choisi parmi les polyamides, les polyesters ; le polypropylène ; le polyéthylène, de préférence « haute densité » ; les dérivés du polyéthylène tels que le polytétrafluoroéthylène, le polyéthylène téréphtalate ; les polyacrylates ; les polyacrylamides ; les méthacrylamides ; les polysulfones ; les polyvinyles, notamment la polyvinylpyrolidone (PVP), le divinylbenzène ; les polysaccharides éventuellement réticulés ; les polylactides et polyglycolides ; les polystyrènes ; les méthylstyrènes ; le dextran ou l'agarose réticulé.

Selon l'invention, on utilisera de préférence un polymère vinylique hydrophile et riche en radicaux hydroxyle (OH), dont la composition atomique est exclusivement constituée de carbone, d'oxygène et d'hydrogène, et dont la polymérisation est totale. Un tel polymère est d'utilisation courante dans la fabrication d'implants et comme constituant de dispositifs médicaux implantables.

Il est également d'utilisation courante au contact de substances chimiques ou biotechnologiques à visée thérapeutique.

Un autre avantage de ce polymère est la disponibilité commerciale de microparticules présentant les caractéristiques techniques et les garanties d'innocuité compatibles avec l'utilisation prévue de l'objet de l'invention.

Les microparticules sont préparées par des procédés usuels décrits dans la littérature, notamment par polymérisation en bloc ou en émulsion.

Dans le cas de la polymérisation en bloc, la solution aqueuse contenant les divers monomères et l'initiateur est soumise à une polymérisation en phase homogène. Le bloc de gel aqueux obtenu est ensuite fractionné en grains, par exemple par passage à travers les mailles d'un tamis.

La polymérisation en émulsion peut fournir directement le gel aqueux sous forme de microparticules de taille déterminée. Elle peut être effectuée par exemple en versant la solution aqueuse contenant les divers monomères dans une phase liquide organique, non miscible à l'eau, maintenue en agitation et contenant éventuellement un agent émulsifiant, puis en introduisant un initiateur de polymérisation.

De tels procédés, qui sont bien connus de l'homme du métier, sont notamment décrits dans la demande EP 040 124.

Une autre technique usuelle dans le domaine est le séchage à contre-courant d'air chaud et sec (« spray drying ») d'un nébulisat de polymère.

Un élément important du bon fonctionnement de l'invention est la nature et les caractéristiques de l'agent de suspension dans lequel les microparticules peuvent être en suspension ou qui peut constituer l'essentiel, voire la totalité, de la composition. Cet agent de suspension peut être un liquide ou un gel.

Cet agent devra permettre de maintenir les particules en suspension dans les conditions normales de conservation et d'utilisation de l'ensemble. A une température et à un pH voisins des conditions de la physiologie, c'est-à-dire un pH compris entre environ 6 et 8 et à une température comprise entre + 25°C et + 40°C, dans des conditions d'isotonicité, ledit agent aura de préférence une densité comprise entre environ 0,85 et 1,35 et une viscosité apparente caractérisée par μ_0 inférieur ou égal à 300 Pa.s et μ_∞ supérieur ou égal à 10 Pa.s (mesurée selon le modèle rhéologique de Herschel-Buckley).

La consistance de l'agent de suspension sera adaptée au mode d'implantation choisi, par exemple permettant une injection intradermique ou sous cutanée.

La consistance du gel devra être aussi proche que possible de celle du tissu vivant dans lequel il est prévu qu'il soit implanté. Cette consistance variera par exemple entre celle d'un tissu conjonctif pour le moins ferme et celle du cartilage pour le plus ferme. Un façonnage préalable à une implantation chirurgicale plus invasive pourra être réalisé par moulage seul ou complété (tranché, poli, râpé, scié, ...) par utilisation des instruments chirurgicaux habituels.

En principe, tout type de liquide ou de gel biocompatible, peu ou pas résorbable, compatible avec la nature des microparticules peut convenir. Dans le cas d'un gel, celui-ci peut éventuellement être partiellement ou totalement réticulé.

Dans ce cas, la porosité dudit agent de suspension, évaluée par l'espace moyen entre les noeuds de réticulation sera telle qu'elle exclut la pénétration d'éléments figurés ayant un poids moléculaire supérieur à 1 000 kilodaltons.

Une caractéristique particulièrement avantageuse de la présente invention consiste dans l'utilisation d'un agent de suspension, de préférence un gel, dont la charge électrique sera globalement positive.

En effet, les macromolécules fibrillaires assurant une liaison physique entre les microsphères portent des charges négatives. Dans un milieu globalement neutre, la diffusion de ces molécules serait seulement passive, et donc lente et limitée.

Les charges positives présentes au sein de l'agent de suspension, de préférence un gel, auront au contraire un effet attractif pour ces macromolécules, assurant une diffusion active plus rapide et favorisant des concentrations élevées dans l'ensemble de la masse de l'agent de suspension.

Le rapprochement macromolécules fibrillaires et microparticules sera ainsi favorisé. Une charge globale négative de l'agent de suspension aurait bien entendu un effet opposé.

L'agent de suspension peut également contenir une ou plusieurs substances pharmacologiquement actives, en particulier un agent analgésique ou anti-inflammatoire.

Le contrôle d'une charge électrique différentielle entre l'implant et le milieu extérieur peut être exploité pour contrôler le taux de diffusion centrifuge ou centripète de substances vers ou en provenance de l'implant, en particulier dans le cas de la délivrance de substances pharmacologiquement actives.

De plus, l'utilisation d'un agent de suspension, de préférence un gel, portant une charge électrique globalement positive présente l'avantage d'éviter les calcifications au niveau du site d'implantation.

Selon un aspect ultérieur de l'invention, un agent de suspension dont la porosité et/ou la charge positive globale sont telles que définies ci-dessus peut être utilisé à lui seul pour la fabrication d'un implant hétérologue histocompatible.

Selon l'invention, on peut utiliser comme agent de suspension des solutions ou gels constitués ou contenant une solution de polymères d'origine naturelle, tels que par exemple les celluloses, les celluloses modifiées et leur dérivés, comme par exemple la carboxyméthylcellulose, ou encore les polysaccharides cationiques d'origine naturelle, biotechnologique ou synthétique, comme par exemple la chitine, le chitosane et leurs dérivés tels que les dérivés carboxyméthyl-, carboxyéthyl-, N-acyl-, N-carboxyalkyl-, N-carboxyacyl, O-carboxyalkyl, hydroxyalkyl et leurs sels.

Dans un aspect avantageux, on utilisera une solution aqueuse desdits polymères.

Une solution aqueuse de chitosane à 3 % et réticulée, par exemple par un aldéhyde, convient parfaitement à l'application de l'invention à un implant intradermique.

Toutefois, des molécules d'origine naturelle telles que le chitosane sont incompatibles avec des méthodes de stérilisation par rayonnement gamma, ce qui en limite l'utilisation à des dispositifs préparés aseptiquement plutôt que stériles.

Une forme avantageuse de l'invention consiste en l'utilisation d'un gel synthétique, par exemple un polymère d'acrylamide substitué ou non, de vinylpyrrolidone, d'acrylate d'hydroxyalkyle ou un copolymère d'acrylamide substitué ou non substitué et d'une autre molécule portant une charge électrique positive tel qu'un monomère cationique ammonium quaternaire tel que, par exemple, des monomères de type diallyldiméthylammonium, (2-(méthacryloylamino)-propyl) triméthylammonium, (2-(méthacryloyloxy)éthyl)triméthylammonium ou (2-acryloyloxy)éthyl triméthylammonium disponibles commercialement. La préparation de tels polymères ou copolymères par des techniques usuelles de polymérisation sont décrits dans la littérature. Le composé préféré dans le cadre de la présente invention est un gel faiblement réticulé de poly(acrylamide-*co*-diallyldiméthylammonium).

Ce composé dont la biocompatibilité a été montrée conformément aux spécifications de la norme ISO EN 10993 présente l'avantage d'une grande modularité, en fonction de sa concentration et de son taux de réticulation.

Il est en outre parfaitement stérilisable par rayonnement gamma à des doses stérilisatrices égales ou supérieures à 25 kgy.

Il peut facilement être obtenu avec des tailles de maille reproductibles et homogènes, selon des techniques bien connues de l'homme du métier.

La diffusion active des macromolécules fibrillaires à travers la matrice de ce gel est donc parfaitement assurée de façon également reproductible et fiable, tout en empêchant la diffusion de cellules entières, limitant ainsi au minimum des éventuelles réactions inflammatoires de type dit « à corps étranger ».

Un autre objet de la présente invention est donc de fournir un implant biocompatible, facilement injectable, procurant une augmentation tissulaire durable, et dont les risques de migration à distance du site d'implantation sont limités au minimum.

Selon un de ses aspects, l'invention concerne donc également un implant hétérologue histocompatible comprenant une composition telle que décrite ci-dessus.

Elle concerne également un implant hétérologue histocompatible comprenant un agent de suspension ayant les caractéristiques définies plus haut.

L'invention a également pour objet l'utilisation de ladite composition ou de l'agent de suspension tel que défini plus haut pour la fabrication d'un implant hétérologue histocompatible, ledit implant étant en particulier utilisable en chirurgie plastique, esthétique, reconstructrice et urologique.

Ladite composition ou ledit agent de suspension peuvent, selon un aspect préféré de l'invention, être utilisés pour fabriquer une prothèse mammaire injectable. Les prothèses mammaires injectables contenant ladite composition ou ledit agent de suspension représentent un aspect ultérieur de l'invention.

En résumé, la présente invention permet le développement et l'utilisation de matériaux implantables assurant un ancrage durable et atraumatique dans la matrice extracellulaire en particulier.

L'invention est illustrée par les exemples ci-après :

EXEMPLE 1

Gel injectable par voie intradermique pour la correction durable de rides et de dépressions cicatricielles, du galbe des lèvres, etc...

. microparticules d'acétate de polyvinyle (HW-55F, Sigma Aldrich Fine Chemicals réf 8-07457)	200 mg
. acrylamide	35 mg
. bis acrylamide	1,75 mg
. diallyldiméthylammonium (DADMA)	2 mg
. eau ppi	qsp 1 ml.

Des corrections superficielles fines, y compris de lésions de type « vergéture », seront effectuées avec une préparation de l'Exemple 1 ou mieux de l'Exemple 2 ci-dessous.

Ces mêmes compositions sont aussi particulièrement adaptées aux techniques de resurfaçage parfois nécessaires après un traitement par lipoaspiration et pour lesquelles l'injection de graisse autologue est un palliatif imparfait.

EXEMPLE 2

Gel injectable comme à l'exemple 1, mais destiné à une correction réversible dans le temps

. microparticules d'acétate de polyvinyle (HW-55F, Sigma Aldrich Fine Chemicals réf 8-07457)	200 mg
. chitosane stabilisé	20 mg
. tampon PB	qsp 1 ml.

La composition du tampon PB est la suivante :

- Chlorure de magnésium ($MgCl_2$, 4,5 H_2O)	0,1763 g
- Dihydrogénophosphate de sodium (NaH_2PO_4)	0,0358 g
- Disodium hydrogénophosphate (Na_2HPO_4, $12H_2O$)	0,2758 g
- Chlorure de sodium (NaCl)	8,7660 g
- Eau ppi : qsp	1 000 ml

La formule de l'exemple 2 permet une correction durable par apport des microparticules non-résorbables ; toutefois, le chitosane est, lui, résorbable et représente environ 50 % du volume initial de l'implant ; le volume résiduel sera donc environ la moitié du volume initial.

Une variante ne contenant pas de microparticules permettra une correction transitoire dont la durée sera limitée à environ 1 an, et devra être renouvelée. Elle sera particulièrement indiquée dans le cas de sites évolutifs, un amaigrissement par exemple pouvant rendre un implant non-résorbable visible et disgracieux. Elle constitue le complément idéal des implants définitifs, ceux-ci ne devant pas apporter une correction totale et en aucun cas une sur-correction.

EXEMPLE 3

Une variante de l'exemple 1 comportant une plus forte concentration, en particulier de l'agent réticulant, sera particulièrement adaptée au traitement de l'incontinence urinaire, toujours par voie injectable intratissulaire.

. microparticules d'acétate de polyvinyle

(HW-55F, Sigma Aldrich Fine Chemicals réf 8-07457)	300 mg
. acrylamide	40 mg
. bis acrylamide	2,5 mg
. DADMA	3 mg
. eau ppi	qsp 1 ml.

EXEMPLE 4

Kit pour correction peu invasive d'hypoplasie mammaire.

Afin de respecter des consistances et des sensations au toucher proches de la normale, autorisant en particulier la continuation de l'autocontrôle par palpation, et de ne pas interférer sensiblement avec les méthodes connues d'imagerie médicale éventuellement prescrites par la suite, les compositions et techniques suivantes sont préférées :

- pour injection au contact du plan musculaire supérieur :

. microparticules d'acétate de polyvinyle (HW-55F, Sigma Aldrich Fine Chemicals réf 8-07457)	30 g
. acrylamide	4 g
. bis acrylamide	200 mg
. DADMA	200 mg
. eau ppi	qsp 100 ml.

- pour injection au plan sous-glandulaire et superficiel :

. microparticules d'acétate de polyvinyle (HW-55F, Sigma Aldrich Fine Chemicals réf 8-07457)	15 g
. acrylamide	3 g
. bis acrylamide	120 mg
. DADMA	150 mg
. eau ppi	qsp 100 ml.

REVENDICATIONS

1. Composition comprenant :

- des microparticules poreuses dont le diamètre des pores exclut la pénétration d'éléments figurés ayant un poids moléculaire supérieur à 1000 kilodaltons, et

- un agent de suspension biocompatible.

2. Composition selon la revendication 1, caractérisée en ce que les microparticules sont constituées d'un polymère biocompatible.

3. Composition selon l'une des revendications 1 ou 2, caractérisée en ce que les microparticules ont une forme sphérique ou ovoïde de diamètre supérieur à environ 10 μm, de préférence compris entre 30 μm et 100 μm, en particulier entre 30 et 60 μm.

4. Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce que les microparticules ont des pores dont le diamètre exclut la pénétration d'éléments figurés ayant un poids moléculaire compris entre 0,5 kilodalton et 5 000 kilodaltons, de préférence entre 1 kilodalton et 1 000 kilodaltons.

5. Composition selon l'une quelconque des revendications 1 à 4, caractérisée en ce que les microparticules sont présentes dans la composition à raison d'environ 0,1% à 75% en poids, de préférence d'environ 10% à 40%.

6. Composition selon l'une quelconque des revendications 1 à 5, caractérisée en ce que les microparticules sont constituées d'un polymère vinylique hydrophile riche en radicaux hydroxyles.

7. Composition selon l'une quelconque des revendications 1 à 5, caractérisée en ce que les microparticules sont constituées d'un polymère choisi parmi les polyamides, les polyesters ; le polypropylène ; le polyéthylène,; les dérivés du polyéthylène; les polyacrylates ; les polyacrylamides ; les méthacrylamides ; les polysulfones ; les polyvinyles, notamment la polyvinylpyrolidone, le divinylbenzène ; les polysaccharides éventuellement réticulés ; les polylactides et polyglycolides ; les polystyrène ; les méthylstyrènes ; le dextran ou l'agarose réticulé.

8. Composition selon l'une quelconque des revendications 1 à 7, caractérisée en ce que l'agent de suspension est un liquide ou un gel constitué d'un polymère biocompatible.

9. Composition selon la revendication 8, caractérisée en ce que l'agent de suspension est un gel partiellement ou totalement réticulé dont la porosité exclut la pénétration d'éléments figurés ayant un poids moléculaire supérieur à 1000 kilodaltons.

10. Composition selon la revendication 8 ou 9, caractérisée en ce que l'agent de suspension a une charge électrique globalement positive.

11. Composition selon l'une des revendications 8 à 10, caractérisée en ce que l'agent de suspension est un liquide ou un gel constitué ou contenant une solution de polymères d'origine naturelle choisi parmi les celluloses, les celluloses modifiées et leur dérivés, les polysaccharides cationiques d'origine naturelle, biotechnologique ou synthétique, tels que la chitine, le chitosane , leurs dérivés et leurs sels.

12. Composition selon l'une quelconque des revendications 8 à 10, caractérisée en ce que l'agent de suspension est un liquide ou un gel choisi parmi les polymères d'acrylamide substitué ou non, de vinylpyrrolidone, d'acrylate d'hydroxyalkyle ou les copolymères d'acrylamide substitué ou non substitué et d'une autre molécule portant une charge électrique positive telle qu'un monomère cationique ammonium quaternaire.

13. Composition selon la revendication 12, caractérisée en ce que l'agent de suspension est un gel de poly(acrylamide-*co*-diallyldiméthylammonium) faiblement réticulé.

14. Composition selon l'une quelconque des revendications 1 à 14, caractérisée en ce que l'agent de suspension contient une ou plusieurs substances pharmacologiquement actives.

15. Utilisation d'une composition selon l'une quelconque des revendications 1 à 14 ou d'un agent de suspension selon l'une quelconque des revendications 9 à 14 pour la fabrication d'un implant hétérologue histocompatible.

16. Utilisation selon la revendication 15 pour la fabrication d'un implant hétérologue solide histocompatible utilisable en chirurgie plastique, esthétique, reconstructrice ou urologique.

17. Utilisation selon la revendication 16 pour la fabrication d'une prothèse mammaire injectable.

18. Implant hétérologue histocompatible comprenant une composition selon l'une quelconque des revendications 1 à 14.

19. Implant hétérologue histocompatible comprenant un agent de suspension constitué d'un polymère biocompatible selon l'une quelconque des revendications 9 à 14.

20. Prothèse mammaire injectable comprenant une composition selon l'une quelconque des revendications 1 à 14 ou un agent de suspension constitué d'un polymère biocompatible selon l'une quelconque des revendications 9 à 14.

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REPUBLIQUE FRANÇAISE

INSTITUT NATIONAL
de la
PROPRIETE INDUSTRIELLE

RAPPORT DE RECHERCHE PRELIMINAIRE

établi sur la base des dernières revendications déposées avant le commencement de la recherche

N° d'enregistrement national

FA 564412
FR 9814679

DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie	Citation du document avec indication, en cas de besoin, des parties pertinentes	Revendications concernées de la demande examinée
X	US 5 336 263 A (ERSEK ROBERT A ET AL) 9 août 1994 (1994-08-09) * colonne 3, ligne 9 - colonne 4, ligne 18 * * colonne 5, ligne 17 - colonne 6, ligne 8 * * colonne 7, ligne 17 - colonne 8, ligne 13 * * exemple 1 *	1-8,12, 14-20
X	DATABASE WPI Section Ch, Week 8221 Derwent Publications Ltd., London, GB; Class A11, AN 82-42503E XP002110800 & JP 57 063302 A (MOTOSATO Y), 16 avril 1982 (1982-04-16) * abrégé *	1,2,4,7, 8,11
X	DATABASE WPI Section Ch, Week 9125 Derwent Publications Ltd., London, GB; Class B04, AN 91-180992 XP002110801 & JP 03 108661 A (KURITA WATER IND LTD), 8 mai 1991 (1991-05-08) * abrégé *	1-4,7,8
X	EP 0 073 593 A (DU PONT) 9 mars 1983 (1983-03-09) * page 4, ligne 7 - page 6, ligne 15 *	1,2,4, 7-9
A	EP 0 730 847 A (MENLO CARE INC) 11 septembre 1996 (1996-09-11) * abrégé * * revendications *	1,2,7-9

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DOMAINES TECHNIQUES RECHERCHES (Int.Cl.6)

A61L
A61F

Date d'achèvement de la recherche	Examinateur
3 août 1999	Muñoz, M

CATEGORIE DES DOCUMENTS CITES

- X : particulièrement pertinent à lui seul
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DOCUMENTS CONSIDERES COMME PERTINENTS		Revendications concernées de la demande examinée
Catégorie	Citation du document avec indication, en cas de besoin, des parties pertinentes	
A	WO 93 15721 A (HUBBARD WILLIAM G) 19 août 1993 (1993-08-19)	

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Date d'achèvement de la recherche	Examinateur
3 août 1999	Muñoz, M

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PTO 04-1609

French Patent No. 2 785 811

COMPOSITION COMPRISING POROUS MICROPARTICLES AND A SUSPENSION AGENT, AND ITS USE AS IMPLANT

Jean Louis Bisson

UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. FEBRUARY 2004
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List of the documents cited in the preliminary search report:	Refer to the end of the present specification

COMPOSITION COMPRISING POROUS MICROPARTICLES AND A SUSPENSION AGENT, AND ITS USE AS IMPLANT

[Composition comprenant des microparticules poreuses et un agent de suspension et son utilisation en tant qu'implant]

Inventor:	Jean Louis Bisson
Applicant:	PROCYTECH Company with limited liability

The present invention concerns compositions comprising porous microparticles and/or a suspension agent, where both are biocompatible on the cellular, tissue, or general level, and usable for implantation in a tissue, in particular to increase the volume of this tissue ("soft tissue augmentation"), notably in view of correcting in a lasting manner a deficit in the appearance or the function of this tissue or organ. /1*

The invention relates particularly to plastic and aesthetic surgery, reconstructive surgery, neurological surgery, etc.

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* [The numbers in the right margin indicate the pagination in the original foreign text.]

The use of implants for the correction or the attenuation of lesions of organic or traumatic origin has rapidly and continuously accelerated since the beginning of the 1980s. The standard materials remain collagen and silicone derivatives. Other natural polymers, such as, for example, hyaluronic acid, or synthetics, are becoming increasingly important.

The use of derivatives of animal origin is encountering increasing resistance, first for psychological reasons, and also because the persistence of their effect is temporally limited.

In addition, it is known that compounds of animal origin, such as bovine collagen, cause allergic reactions in approximately 3% of the cases. The frequency and the severity of these reactions are worsened by the need to administer repeated injections, which are necessary to maintain a satisfactory result. The silicone and silicone oil derivatives, although prohibited in some cases, remain among the most used compounds to obtain a lasting effect. However, their use is often associated with local problems (siliconomas) or problems associated with migration, sometimes over considerable distances from the implantation site.

Another known substitution technique consists in injecting microspheres made of various materials (plastic, glass, ceramics, ...) into the tissues. In general, these particles have a size which is greater than the limit (phagocytosis) of absorption by the monocytes which will form a fibrous film on their surface to insulate the particles from the surrounding tissues. Such particles are described, for example, in US Patent 5,344,452.

The result of these injections is generally lasting, but it is known that the particles can migrate over some distance from their implantation site, resulting in the complication of a risk due to obstruction of the microvascular structures, which can result in ischemia or embolism.

It has now been found that by using microparticles presenting a controlled porosity and/or a suspension agent, for example, in the form of a gel, one can obtain the penetration of /2
protein and/or glycan fibrils of the implanted tissues, allowing a micro-fibrillar matrix anchoring which significantly limits the risks of migration at a distance from the implantation site.

The object of the invention, therefore, is a composition comprising:

- porous microparticles whose pore diameter excludes the penetration of figured elements having a molecular weight of more than 1000 kilodalton, and

- a biocompatible suspension agent.

The solid component of the composition according to the invention consists of biocompatible porous microparticles.

The microparticles which are used in the composition according to the invention preferably have a spherical or ovoid form, and a diameter of more than approximately 10 μm, in particular a diameter of 30-100 μm, preferably 30-60 μm.

When the microparticles are not spherical, the term "diameter" is understood to refer to the largest diameter of the surface area having the smallest transverse cross section.

Particles having a size of less than 10 μm would be easily entrained, actively or passively, at a distance from their implantation site.

Conversely, the use of particles having a size greater than approximately 1000 μm would risk giving the tissues a visually perceivable roughness or a roughness which can be felt by touching in the case of a superficial implantation. In addition, it would be more difficult to inject the product through a needle with small diameter, for example, 30G, as required for an atraumatic procedure.

An advantageous characteristic of the microparticles which can be used according to the invention is that they present an imperfectly rigid structure, allowing a slight deformation in case of compression. The expression "imperfectly rigid structure" denotes a structure such that when exposed to the action of an axial compression having a maximum value which is compatible with the resistance of the surrounding living tissue (less than or equal to approximately 3 kg/cm^2), the particles will not break and their rate of deformation along this axis will be 0-40%. This deformation will limit the tendency of the particles to move, a phenomenon which is known in the case of rigid particles by the name of "melon pip effect."

The microparticles which can be used according to the invention, and which can make up most of the composition, present a porous structure. The diameter of the pores is determined so as to exclude the penetration of the particles by figured elements having a size of more than 1000 kilodalton. A porosity is sought which is such that it promotes the penetration of macromolecules having a naturally present structure into the tissues surrounding the implant. These macromolecules, in particular elastin, collagen or glycosaminoglycans (GAGs), which are of a microfibrillar nature, form an intricate network which connects the microparticles which they penetrate. /3

In particular, the microparticles have pores whose diameter excludes the penetration of figured elements having a molecular weight of 0.5-5000 kilodalton, preferably 1-1000 kilodalton.

The anchoring system so obtained forms a flexible and elastic structure whose coherence is accentuated over time as an increasing number of microfibrillar links ensures its crosslinking. The solidity and the consistency of the structure so obtained resemble those of the extracellular matrix, thus ensuring optimal comfort and appearance.

This flexible and deformable consistency of the elements, as of the entire assembly, ensures a minimum risk of trauma which generates lesions and infection of the tissues.

It is preferred for the microparticles to be present in the composition in the amount of approximately 0.1-75 wt%, preferably 10-40 wt%, where the percentages are expressed with reference to the total weight of the composition.

The material which constitutes the microparticles will be cyto- and histocompatible, and more generally, biocompatible by the definition of the standard ISO EN 10993. It is preferably a polymer whose starting monomers do not present any character of toxicity which is incompatible with the considered use.

For example, one can use a polymer chosen from the polyamides, the polyesters; polypropylene; polyethylene, preferably "high density;" the derivatives of polyethylene such as polytetrafluoroethylene, polyethylene terephthalate; the polyacrylates; the polyacrylamides; the methacrylamides; the polysulfones; the polyvinyls, notably polyvinylpyrolidone (PVP), divinylbenzene; the optionally crosslinked polysaccharides; the polylactides and polyglycolides; the polystyrenes; the methylstyrenes; dextran or crosslinked agarose.

According to the invention, it is preferred to use a hydrophilic vinyl polymer which is rich in hydroxyl radicals (OH), whose atomic composition exclusively consists of carbon, oxygen and hydrogen, and whose polymerization is complete. Such a polymer is routinely used in the manufacture of implants and as a constituent of implantable medical devices.

It is also routinely used in contact with chemical or bioengineered substances which /4
have a therapeutic use.

Another advantage of this polymer is the commercial availability of microparticles which present the technical characteristics and the guarantees of safety which are compatible with the intended use of the object of the invention.

The microparticles are prepared by the usual procedures described in the literature, notably by block or emulsion polymerization.

In the case of block polymerization, the aqueous solution containing the different monomers and the initiator is subjected to a polymerization in a homogenous phase.

The block of aqueous gel obtained is then fractioned into grains, for example, by being passed through the meshes of a sieve.

The emulsion polymerization can directly yield the aqueous gel in the form of microparticles having a predetermined size. It can be carried out, for example, by pouring the aqueous solution containing the various monomers into an organic, water-immiscible, liquid phase, which one continues to stir, and which may optionally contain an emulsifier, followed by the introduction of a polymerization initiator.

Such methods, which are well known to the person skilled in the art, are notably described in application EP 040 124.

Another conventional technique in the field is drying with countercurrent flow of hot and dry air ("spray drying") of a polymer mist.

Important factors in the proper function of the invention are the nature and the characteristics of the suspension agent in which the microparticles can be suspended or which can constitute most, if not all, of the composition. This suspension agent can be a liquid or a gel.

This agent will have to make it possible to maintain the particles in suspension under normal conditions of storage and use of the entire assembly. At a temperature and a pH which approximate physiological conditions, that is a pH of approximately 6-8 and a temperature of +25°C to +40°C, and under conditions of isotonicity, said agent will preferably have a density of approximately 0.85-1.35 and an apparent viscosity characterized by μo being less than or equal to 300 Pa·s and μ_∞ greater than or equal to 10 Pa·s (measured according to the rheological model of Herschel-Buckley).

The consistency of the suspension agent will be adapted to the implantation procedure used, for example, to allow intradermal or subcutaneous injection.

The consistency of the gel should be as close as possible to that of the living tissue into /5
which it is to be implanted. This consistency will vary, for example, between that of a conjunctive tissue, as a less firm tissue, and that of cartilage, as a firmer tissue. A shaping, prior to a more invasive surgical implantation, can be achieved by molding alone, or it can be completed (cutting, polishing, filing, sawing, ...), using the usual surgical instrument.

In principle, any type of biocompatible liquid or gel, with varying degrees of capacity for absorption, which is compatible with the nature of the microparticles, can be appropriate. In the case of a gel, the latter can optionally be partially or completely crosslinked.

In this case, the porosity of said suspension agent, evaluated by the mean spacing between the crosslinking nodes will be such that it excludes the penetration of figured elements having a molecular weight of more than 1000 kilodalton.

A particularly advantageous characteristic of the present invention consists of the use of a suspension agent, preferably a gel, whose overall electrical charge is positive.

Indeed, the fibrillar macromolecules ensure a physical bond between the microspheres which carry negative charges. In an overall neutral medium, the diffusion of these molecules would be only passive, and thus slow and limited.

On the other hand, the positive charges which are present in the suspension agent, preferably a gel, will have an attractive effect on these macromolecules, ensuring a more rapid active diffusion and promoting high concentrations in the overall composition of the suspension agent.

The fibrillar macromolecules and microparticles will thus be promoted to move toward each other. An overall negative charge of the suspension agent would naturally have the opposite effect.

This suspension agent can also contain one or more pharmacologically active substances, in particular an analgesic or an anti-inflammatory.

The control of a differential electrical charge between the implant and the external environment can be exploited to determine the rate of centrifugal or centripetal diffusion of substances toward or from the implant, in particular in the case of the delivery of pharmacologically active substances.

In addition, the use of a suspension agent, preferably a gel, which carries an overall positive electrical charge, presents the advantage of avoiding calcifications at the implant site.

According to another aspect of the invention, a suspension agent whose porosity /6
and/or overall positive charge are as defined above can be used alone for the manufacture of a histocompatible heterologous implant.

According to the invention, one can use, as a suspension agent, solutions or gels consisting of or containing a solution of polymers of natural origin, such as, for example, the celluloses, the modified celluloses and their derivatives, such as, for example, carboxymethylcellulose, or the cationic polysaccharides of natural, bioengineered or synthetic origin, such as, for example, chitin, chitosan, and their derivatives, such as the carboxymethyl, carboxyethyl, N-acyl, N-carboxyalkyl, N-carboxyacyl, O-carboxyalkyl, hydroxyalkyl derivatives and their salts.

According to an advantageous aspect, one uses an aqueous solution of said polymers.

A 3% chitosan aqueous solution, crosslinked, for example, by an aldehyde, is perfectly well suited for the application of the invention in an intradermal implant.

However, molecules of natural origin, such as chitosan, are incompatible with sterilization methods by gamma radiation, which limits their use to devices which are prepared under aseptic, rather than sterile, conditions.

An advantageous form of the invention consists of the use of a synthetic gel, for example, a polymer of substituted or unsubstituted acrylamide, of vinylpyrrolidone, of hydroxyalkyl acrylate or a copolymer of substituted or unsubstituted acrylamide and another molecule carrying a positive electric charge, such as a quaternary ammonium cationic monomer, for example, monomers of the types diallyldimethylammonium, (2-methylacryloylamino)propyl)trimethylammonium, (2-(methacryloyloxy)ethyl)trimethylammonium or (2-acryloyloxy)ethyl trimethylammonium, which are commercially available. The preparation of such polymers or copolymers by the conventional polymerization techniques are [sic; is] described in the literature. The preferred compound in the context of the present invention is a weakly crosslinked gel of poly(acrylamide codiallyldimethylammonium).

This compound, whose biocompatibility has been shown to be in conformity with the specifications of the standard ISO EN 10993, presents the advantage of a high degree of modularity, as a function of its concentration and its crosslinking rate.

In addition, it can be perfectly sterilized by gamma radiation at sterilization doses equal to or greater than 25 kgy.

It can also be obtained with reproducible and homogeneous mesh sizes, using techniques /7
which are well known to the person skilled in the art.

The active diffusion of fibrillar macromolecules through the matrix of this gel is thus perfectly ensured, in a reproducible and reliable manner, while preventing the diffusion of whole cells, thus limiting so-called "foreign body" inflammatory reactions to a minimum.

Another object of the present invention is thus to provide a biocompatible implant which can easily be injected, procures a lasting tissue augmentation and is associated with minimal risks of migration at a distance from the implantation site.

According to one of its aspects, the invention thus also concerns a histocompatible heterologous implant comprising a composition as described above.

It also concerns a histocompatible heterologous implant comprising a suspension agent having the above-defined characteristics.

The invention also relates to the use of said composition or suspension agent as defined above for the manufacture of a histocompatible heterologous implant, said implant being usable, in particular, in plastic, aesthetic, reconstructive and urologic surgery.

Said composition or said suspension agent can, according to a preferred aspect of the invention, be used to manufacture an injectable mammary prosthesis.

The injectable mammary prostheses containing said composition or said suspension agent represent a later aspect of the invention.

In summary, the present invention allows the development and the use of implantable materials ensuring, in particular, a lasting and atraumatic anchoring in the extracellular matrix.

The invention is illustrated by the following examples:

Example 1

Gel which can be injected by the intradermal route for the lasting correction of wrinkles and scar-associated depressions, shape of the lips, etc.

· microparticles of polyvinyl acetate (HW-55F, Sigma Aldrich Fine Chemicals Reference 8-07457)	200 mg
· acrylamide	35 mg
· bisacrylamide	1.75 mg
· diallyldimethylammonium (DADMA)	2 mg

· water ppi qsp 1 mL.

Fine superficial corrections, including lesions of the "stretch mark" type, are made using a preparation of Example 1 or, better, of Example 2 below. /8

The same compositions are also particularly well suited for the resurfacing techniques which are sometimes required after liposuction treatment and for which the injection of autologous fat is an imperfect palliative.

Example 2

Gel which can be injected, as in Example 1, but which is intended for a correction which can be reversed over time.

· microparticles of polyvinyl acetate (HW-55F, Sigma Aldrich Fine Chemicals Reference 8-07457)	200 mg
· stabilized chitosan	20 mg
· PB buffer	qsp 1 mL.

The composition of the PB buffer is as follows:

- Magnesium chloride ($MgCl_4$, 4.5 H_2O	0.1763 g
- Sodium dihydrogenophosphate (NaH_2PO_4)	0.0358 g
- Disodium hydrogenophosphate (Na_2HPO_4, $12H_2O$)	0.2758 g
- Sodium chloride (NaCl)	8.7660 g
- Water ppi: qsp	1000 mL

The formula of Example 2 allows a lasting correction by providing nonadsorbable microparticles; however, chitosan is absorbable and it represents approximately 50% of the initial volume of the implant; the residual volume will thus be approximately half of the initial volume.

A variant which does not contain any microparticles will allow a transient correction, whose duration will be limited to approximately 1 year, and which will be have to be repeated. It is particularly indicated for the case of actively evolving sites, where, for example, weight loss can make an unabsorbable implant visible and unsightly. It constitutes the ideal complement for permanent implants, which should not provide a total correction and most of all should not overcorrect.

Example 3

A variant of Example 1 comprising a stronger concentration, particularly of the crosslinking agent, will be especially adapted to the treatment of urinary incontinence, by the route of intratissue injection.

· microparticles of polyvinyl acetate

(HW-55F, Sigma Aldrich Fine Chemicals Reference 8-07457)	300 mg
· acrylamide	40 mg
· bisacrylamide	2.5 g
· DADMA	3 mg
· water ppi	qsp 1 mL.

/9

Example 4

Kit for low invasive correction of mammary hypoplasia.

To maintain consistency and sensation to the touch--which should be close to normal, in particular they should allow a person to continue self-examination by palpation and they should not substantially interfere with known medical imaging procedures which may be prescribed later–the following compositions and techniques are preferred:

- for injection in contact with the upper muscle level:

· microparticles of polyvinyl acetate	
(HW-55F, Sigma Aldrich Fine Chemicals reference 8-07457)	30 g
· acrylamide	4 g
· bisacrylamide	200 mg
· DADMA	200 mg
· water ppi	qsp 100 mL.

- for injection at the subglandular and superficial level:

· microparticles of polyvinyl acetate	
(HW-55F, Sigma Aldrich Fine Chemicals reference 8-07457)	15 g
· acrylamide	3 g
· bisacrylamide	120 mg
· DADMA	150 mg
· water ppi	qsp 100 mL.

Claims

/10

1. Composition comprising:

- porous microparticles whose pore diameter excludes the penetration of figured elements having a molecular weight of more than 1000 kilodalton, and

- a biocompatible suspension agent.

2. Composition according to Claim 1, characterized in that the microparticles consist of a biocompatible polymer.

3. Composition according to one of Claims 1 or 2, characterized in that the particles have a spherical or ovoid shape with a diameter greater than approximately 10 μm, preferably 30-100 μm, in particular 30-60 μm.

4. Composition according to any one of Claims 1-3, characterized in that the microparticles have pores whose diameter excludes the penetration of figured elements having a molecular weight of 0.5-5000 kilodalton, preferably 1-1000 kilodalton.

5. Composition according to any one of Claims 1-4, characterized in that the microparticles are present in the composition in the amount of approximately 0.1-75 wt%, preferably approximately 10-40 wt%.

6. Composition according to any one of Claims 1-5, characterized in that the microparticles consist of a hydrophilic vinyl polymer rich in hydroxyl radicals.

7. Composition according to any one of Claims 1-5, characterized in that the microparticles consist of a polymer chosen from the polyamides, the polyesters; polypropylene; polyethylene; the derivatives of polyethylene; the polyacrylates; the polyacrylamides; the methacrylamides; the polysulfones; the polyvinyls, notably polyvinylpyrolidone, divinylbenzene; the optionally crosslinked polysaccharides; the polylactides and polyglycolides; the polystyrene [sic; polystyrenes]; the methylstyrenes; dextran or crosslinked agarose.

8. Composition according to any one of Claims 1-7, characterized in that the suspension agent is a liquid agent or a gel consisting of a biocompatible polymer.

9. Composition according to Claim 8, characterized in that the suspension agent is a partially or completely crosslinked gel whose porosity excludes the penetration of figured elements having a molecular weight of more than 1000 kilodalton.

10. Composition according to Claim 8 or 9, characterized in that the suspension agent has an overall positive electrical charge. /11

11. Composition according to one of Claims 8-10, characterized in that the suspension agent is a liquid or a gel consisting of or containing a solution of polymers of natural origin, chosen from the celluloses, the modified celluloses and their derivatives, the cationic polysaccharides of natural, bioengineered or synthetic origin, such as chitin, chitosan, their derivatives and their salts.

12. Composition according to any one of Claims 8-10, characterized in that the suspension agent is a liquid or a gel chosen from the polymers of substituted or unsubstituted acrylamide, of vinylpyrrolidone, of hydroxyalkyl acrylate, or the copolymers of substituted or unsubstituted acrylamide and of another molecule bearing a positive electric charge, such as a quaternary ammonium cationic monomer.

13. Composition according to Claim 12, characterized in that the suspension agent is a weakly crosslinked gel of poly(acrylamide-co-diallyldimethylammonium).

14. Composition according to any one of Claims 1-14, characterized in that the suspension agent contains one or more pharmacologically active substances.

15. Use of a composition according to any one of Claims 1-14 or of a suspension according to any one of Claims 9-14 for the manufacture of a histocompatible heterologous implant.

16. Use according to Claim 15 for the manufacture of a histocompatible solid heterologous implant which can be used in plastic, aesthetic, reconstructive or urologic surgery.

17. Use according to Claim 16 for the manufacture of an injectable mammary prosthesis.

18. Histocompatible heterologous implant comprising a composition according to any one of Claims 1-14.

19. Histocompatible heterologous implant comprising a suspension agent consisting of a biocompatible polymer according to any one of Claims 9-14.

20. Injectable mammary prosthesis comprising a composition according to any one of Claims 1-14 or a suspension agent consisting of a biocompatible polymer according to any one of Claims 9-14.

FRENCH REPUBLIC
National Institute
of Industrial Property

Application Number
FA 564412
FR 9814679

PRELIMINARY SEARCH REPORT

established on the basis of the most recent claims filed before the start of the search

DOCUMENTS CONSIDERED TO BE RELEVANT		Claims concerned in the examined document	
Category	Citation of document with indication where appropriate, of relevant passages		
X	US 5 336 263 A (ERSEK ROBERT A ET AL) August 9, 1994 (1994-08-09) * column 3, line 9 – column 4, line 18 * * column 5, lin3 17 – column 6, line 8 * * column 7, line 17 – column 8, line 13 * * Example 1 * ---	1-8, 12, 14-20	
X	DATABASE WPI Section Ch, Week 8221 Derwent Publications Ltd., London, GB; Class All, AN 82-42503E XP002110800 & JP 57 063302 A (MOTOSATO Y), April 16, 1982 (1982-04-16) * Abstract * ---	1,2,4,7, 8,11	TECHNICAL FIELDS SEARCHED (Int. Cl.6)
X	DATABASE WPI Section Ch, Week 9125 Derwent Publications Ltd., London, GB; Class B04, AN 91-180922 XP002110801 & JP 03 108661 A (KURITA WATER IND LTD), May 8, 1991 (1991-05-08) * Abstract * ---	1-4,7,8	A61L A61F
X	EP 0 073 593 A (DU PONT) Mach 9, 1983 (1983-03-09) * Page 4, line 7 – page 6, line 15 * ---	1,2,4, 7-9	
A	EP 0 730 847 A (MENLO CARE INC) September 11, 1996 (1996-09-11) * Abstract * * Claims * --- -/--	1,2,7-9	

Date of completion of the search	Examiner
August 3, 1999	Muñoz, M

CATEGORY OF CITED DOCUMENTS

X: Particularly relevant if taken alone.
Y: Particularly relevant if combined with another document of the same category.
A: Technological background.
O: Non-written disclosure.
P: Intermediate document.

T: Theory or principle underlying the invention.
E: Earlier patent document, but published on, or after the filing date.
D: Document cited in the application.
L: Document cited for other reasons.

&: Member of the same patent family, corresponding document.

FRENCH REPUBLIC
National Institute
of Industrial Property

Application Number
FA 564412
FR 9814679

SEARCH REPORT

established on the basis of the most recent claims filed before the start of the search

DOCUMENTS CONSIDERED TO BE RELEVANT		Claims concerned in the examined document	
Category	Citation of document with indication where appropriate, of relevant passages		
A	WO 93 15721 A (HUBBARD WILLIAM G) August 19, 1993 (1993-08-19) -----		
			TECHNICAL FIELDS SEARCHED (Int. Cl.6)

Date of completion of the search	Examiner
August 3, 1999	Muñoz, M

CATEGORY OF CITED DOCUMENTS

X: Particularly relevant if taken alone.
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A: Technological background.
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T: Theory or principle underlying the invention.
E: Earlier patent document, but published on, or after the filing date.
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&: Member of the same patent family, corresponding document.

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EXHIBIT B

Use of Porous High-Density Polyethylene Implants in Temporal Contour Reconstruction

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A temporal contour deformity is characterized by a concavity or depression in the soft-tissue contour of the temporal region and is associated with exaggerated relief of the lateral orbital rim and the zygomatic arch. The etiology of the deformity is varied, comprising any condition that results in displacement, atrophy, or absence of the temporalis muscle or the superficial temporal fat pad. We describe reconstruction of this deformity with porous high-density polyethylene implants in 16 consecutive patients, treated between July 1988 and September 1990. The etiology of the deformity and the surgical treatment are described. The results of treatment are assessed on long-term follow-up, ranging from 2 to 4 years postoperatively.

Key Words: Polyethylene implant, temporal contour

The temporal fossa is circumscribed by the zygomatic arch inferiorly, the temporal ridge of the skull superiorly, and the lateral orbital rim anteriorly. Normally, this space is occupied by the temporalis muscle and the superficial temporal fat pad, providing a smooth, convex, soft-tissue contour. Diminution in the volume of the soft tissues within the temporal fossa produces a temporal contour deformity, characterized by an obvious depression in the soft-tissue contour and exaggerated relief of the lateral orbital rim and the zygomatic arch.

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The etiology of the deformity is varied, comprising any condition that results in displacement or atrophy of the temporalis muscle or the superficial temporal fat pad. Temporal contour defects have previously been described as a donor site deformity following transfer of the temporalis muscle for coverage or reanimation [1] in patients sustaining ischemic injury and fibrosis of the temporalis muscle following frontotemporal bone flap elevation [2] and in patients with atrophy or prolapse of the superficial temporal fat pad complicating extended coronal flap elevation. (Lacey M, Antonyshyn O, MacGregor JH. Unpublished observations, 1992.)

Reconstruction of the temporal contour deformity aims to obliterate the defect by subcutaneous or submuscular placement of an implant, which augments the deficient temporal soft-tissue volume. The optimal material for this application must be easily carved into a three-dimensional shape, and must maintain its shape, volume, and position in vivo. Although we prefer to use autogenous bone, limited graft availability in these patients, who often require extensive bone grafting for other facial skeletal defects, prompted us to search for a suitable alloplastic material.

Porous high-density polyethylene (PHDPE) (Medpor; Porex Medical, Atlanta, GA) provides the standard of biocompatibility against which other compounds are measured because of its long-term stability and virtual lack of an inflammatory or foreign-body response [3]. Animal histological studies have documented rapid vascular, connective tissue, and bony ingrowth into the implant [4], which provide a stable interface that firmly anchors the implant, particularly when it is placed adjacent to bone. Most importantly, the mechanical properties of PHDPE (high tensile strength, noncompressible, stress- and fatigue-resistant) are such that the volume and shape of an implant are maintained in vivo, with no subsequent degradation or deformation [5].

We describe our experience with the use of PHDPE implants in the reconstruction of temporal contour deformities.

Materials and Methods

Patients

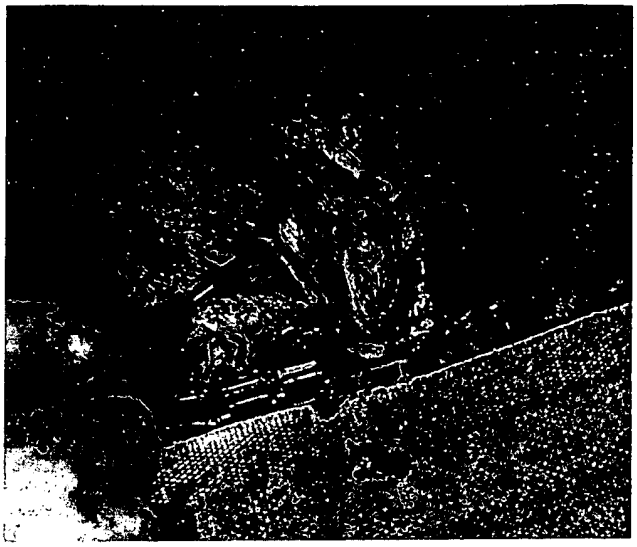
All patients with temporal contour deformities presenting to the Plastic Surgery Clinic at Dalhousie University between July 1988 and September 1990 were included in the study. The clinical series comprises 16 consecutive patients. There were 5 women and 11 men, whose average age was 34 years.

The various causes of contour deformity, as observed in this population, are listed in the Table. In most patients, the deficit in temporal soft-tissue volume occurred as a direct consequence of a planned surgical procedure, and could therefore be anticipated and reconstructed primarily. All patients undergoing temporalis muscle transfer for coverage or reanimation underwent immediate obliteration of the donor site defect with a contoured PHDPE implant. In 5 patients

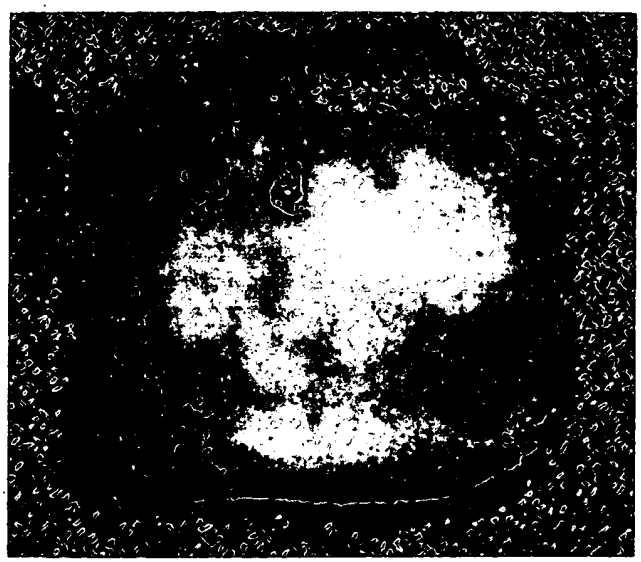
Etiology of Temporal Contour Deformity

Etiology	*No. Patients*
Donor site deformity following temporalis muscle transfer	4
Excision of superficial temporal fat pad (orbitotemporal neurofibroma)	5
Atrophy/displacement of superficial temporal fat pad complicating extended coronal flap elevation	7

A



B



C

Fig 1 Secondary reconstruction of right temporal contour deformity. Intraoperative views following reflection of coronal flap. (A) Depression in the right temporal area due to superficial fat pad atrophy. (B) An incision is made through the temporalis muscle, parallel to muscle fibers. A subperiosteal pocket is dissected deep to the muscle, taking care to maintain muscle attachments to the temporal ridge of the skull. (C) Carved porous high-density polyethylene implant. The volume and shape of the implant must provide thorough adaption to the underlying temporal fossa while correcting the soft-tissue deficit.

with orbital neurofibromas, preoperative magnetic resonance imaging (MRI) revealed tumor infiltrating the superficial temporal fat pad and hypoplasia of the underlying temporalis muscle. Intraoperatively, the volume deficit resulting from radical excision of the neurofibroma was reconstructed immediately with a subtemporal implant.

Seven patients in the series presented with a temporal contour deformity as a complication of extended coronal flap elevation. MRI investigations confirmed that the defect was due to atrophy or prolapse of the superficial temporal fat pad, rather than any change in temporalis muscle bulk.

Surgical Technique

Although causes of the temporal contour deformity are varied, treatment options are dependent on whether there is functioning temporalis muscle present in the fossa. If present, contour augmentation is performed by submuscular placement of the implant.

The approach to the temporal fossa is through a bicoronal flap incision. The dissection is carried down to the deep temporal fascia; the temporalis muscle is split in the direction of its fibers, and the muscle is elevated off the temporal fossa subperiosteally in an area corresponding to the defect. Care should be taken to avoid dissection of the attachment of muscle fibers to the temporal ridge of the skull (Fig 1).

A PHDPE implant of the appropriate size is then carved to the shape required for contour augmentation. Soaking the implant in a warm, sterile solution further facilitates bending of the implant for more accurate adaptation to the underlying calvarial surface. Prior to implantation, the implant is soaked in antibiotic solution.

The implant is inserted into the subperiosteal pocket, deep to the temporalis muscle. It is important to ensure that the deep surface of the implant conforms accurately to the contours of the underlying temporal bone and that its position is stable. The longitudinal incision in the deep temporal fascia is then closed with absorbable suture.

Some variations on this technique are possible. To prevent early migration of the implant, particularly if its position is subcutaneous rather than submuscular, it can be rigidly stabilized with lag-screw fixation to the lateral orbital rim or wall. If only part of the temporalis muscle is transferred, then the posterior portion of the muscle is transposed anteriorly to cover the alloplast and is then sutured to the lateral orbital rim.

If the PHDPE implant must be placed subcutaneously because of a lack of temporalis muscle, careful consideration must be given to precise shaping and feathering of the implant to ensure that its borders are not visible or palpable (Fig 2).

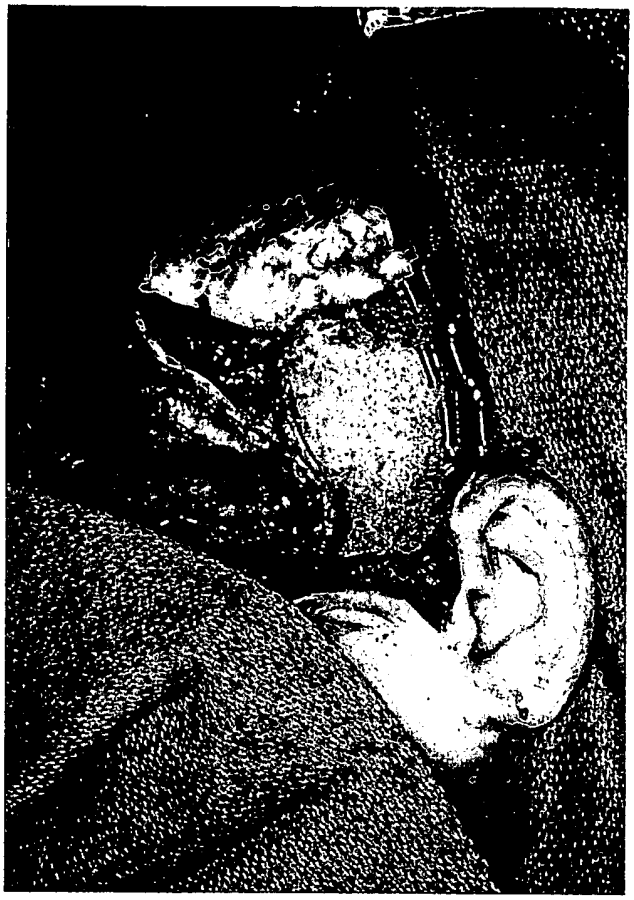


Fig 2 Primary reconstruction of left temporal donor site contour deformity following total temporalis muscle transfer. Because the implant is entirely subcutaneous, precise shaping and peripheral feathering are particularly important. The implant occupies the entire temporal fossa.

Results

Sixteen patients underwent reconstruction of a temporal contour deformity with PHDPE implants. The implant was placed in a submuscular pocket in 12 patients, and in a subcutaneous pocket in the remaining 4 patients.

Submuscular implantation consistently produced the best aesthetic result (Fig 3). The contour deficit was effectively obliterated in all patients, and the implant remained entirely invisible. The overlying temporalis muscle remained active and effectively obscured the margins of the implant, providing a natural contour even during mastication.

Subcutaneous implants, although effective in obliterating the defect, produced a firm, nonyielding, and adynamic temporal contour. The margins of the implant were always palpable, and in 1 patient were clearly visible.

A B

Fig 3 Right temporal contour deformity correction with a submuscular implant. (A) Preoperative view. (B) Result, 3 months' postoperatively.

In this series, stabilization of the implant relied on accurate adaptation of the deep surface of the implant to the calvarial surface and limited dissection of a subperiosteal pocket. Rigid fixation with lag-screws was employed in only 2 patients.

Early migration of an implant was documented in 1 patient, which was attributed to technical error. In this patient, the anterior half of the temporalis muscle was used to resurface a maxillary defect, whereas the posterior half was advanced to cover the temporal implant. The implant was not contained within a limited "pocket" and was not otherwise secured. In the first postoperative week, it prolapsed behind the posterior edge of the muscle and was clearly displaced. There was no implant instability or migration in the remaining 15 patients.

No other complications were observed in this series during a postoperative follow-up period of 2 to 4 years. There were no infections, interference with temporalis muscle function, or pain associated with any of the implants.

Discussion

Use of PHDPE implants as an alternative to autogenous bone grafting has been previously reported in several clinical trials. This alloplastic material has been successfully employed in cranioplasty [6], augmentation [7], and interpositional [8] genioplasty, and in both acute and delayed reconstruction of traumatic orbital cavity defects [9]. Ease of manipulation, rapid fixation, maintenance of structural integrity, and an absence of implant-related complications have been documented in these various clinical applications of PHDPE implantation.

We review the long-term results of temporal contour reconstruction with PHDPE implants in 16 patients.

This technique was found to be a simple and effective method of correcting a soft tissue volume deficit. With the exception of early implant migration in 1 patient, which can be attributed to technical error, the postoperative course was uneventful, and further complications could not be identified on long-term follow-up.

Presented at the 45th Annual Meeting of the Canadian Society of Plastic Surgeons, June 15, 1991, Whistler, British Columbia.

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ORIGINAL ARTICLE

EXHIBIT C

Porous High-Density Polyethylene Implants in Auricular Reconstruction

James D. Williams, MD; Thomas Romo III, MD; Anthony P. Sclafani, MD; Hyun Cho, MD

Objective: To evaluate the ability of porous high-density polyethylene (Medpor) implants to tolerate exposure and support skin grafts when used to reconstruct defects in auricular cartilage in an animal model.

Design: Polyethylene implants placed in surgically created defects in auricular cartilage and covered with a skin flap were then exposed at either 4, 7, or 21 days after implantation. The exposed implants were then allowed to heal secondarily or received a skin graft 1 week later. The ability of polyethylene implants to tolerate exposure and support skin grafts was observed clinically and via histological study of the implantation sites.

Subjects: Nine adult New Zealand rabbits.

Results: Polyethylene implants demonstrated excellent ability to tolerate wound exposure as early as 4 days after implantation, with extrusion of 1 of the 36 implants placed. The degree of secondary wound healing increased as the interval from implantation to exposure increased from 4 to 21 days. Exposed polyethylene implants in all groups also supported all 18 skin grafts placed 1 week after exposure of the implant surface.

Conclusions: Polyethylene implants are well tolerated as replacements for native cartilage in auricular reconstruction. Polyethylene implants tolerated wound exposure as early as 4 days after implantation and demonstrated the ability to heal by secondary intention and support skin grafts. This is likely because of the extent of fibrovascular ingrowth from surrounding tissue, which allows the material to behave more like native tissue and less like a foreign body in this setting.

Arch Otolaryngol Head Neck Surg. 1997;123:578-583

THE ACCURATE reconstruction of congenital or posttraumatic auricular defects represents an ongoing challenge. Despite remarkable advances in surgical techniques and the handling of both native and artificial graft materials in the last 2 decades, acceptable aesthetic results remain difficult to achieve. The lack of a single preferred material and method for auricular reconstruction is evidenced by the variety of techniques and materials in use. Each technique has disadvantages that limit its use clinically. Soft tissue flaps lack structural support to maintain their size and shape over time. Autologous cartilage is well tolerated in head and neck reconstruction but demands a high level of expertise to accurately carve a realistic framework. There is also the added morbidity of a second operative site to supply the donor cartilage. Cartilage allografts spare the added morbidity of a donor site wound but undergo a variable amount of resorption over time, which can significantly alter the final outcome. Allografts also carry the potential risk of transmissable viral agents.

Because of the inherent shortcomings of cartilage, a number of synthetic materials have been used to substitute for the auricular framework. Biologically inert nonporous substances tend to induce an interface of a vascular capsule between the implant and the recipient tissues. Experience has revealed that infection in this setting is not well tolerated and leads to rapid implant extrusion. Investigations aimed at enhancing the biocompatibility of implant materials have focused largely on the changing nature of the implant-recipient interface. Omori et al[1] report success with silicone-Dacron mesh auricular frameworks, but their results have not been reproduced in other studies. More recently, porous high-density polyethylene

From the Department of Otolaryngology–Head and Neck Surgery (Drs Williams and Sclafani) and the Division of Facial Plastic and Reconstructive Surgery (Dr Romo), The New York Eye and Ear Infirmary, New York, NY; the Department of Otolaryngology–Head and Neck Surgery, New York Medical College, Valhalla (Dr Romo); and the Division of Otolaryngology–Head and Neck Surgery, Beth Israel Medical Center, New York (Dr Cho). *None of the authors holds any financial interests in Porex Surgical Inc or any of its affiliates.*

SUBJECTS AND METHODS

Nine adult, pathogen-free New Zealand rabbits were implanted with three 10×20-mm pieces of 1.5-mm-thick polyethylene and one 10×20-mm piece of 0.5-mm-thick solid silicone (Silastic sheeting model 500-5, Dow Corning Corp, Midland, Mich) to replace surgically excised portions of the native auricular cartilage. The animals were housed separately and given food and water ad libitum. All surgical procedures were performed under sterile operating conditions and with general anesthesia using sodium pentobarbital, 30 mg/kg intraperitoneally, following intramuscular administration of cephalothin sodium, 20 mg/kg.

After induction of the anesthesia, the rabbits were placed in a supine position to allow access to the ventral surface of each ear. They were then prepared with povidone iodine solution on all exposed auricular surfaces. An incision was made 0.5 cm from the lateral border of the ear extending from the base of each ear to a point 1.5 cm from the distal tip (**Figure 1**). The incision was carried down to the depth of the auricular cartilage. A skin-perichondrium flap was then elevated off the auricular cartilage to provide wide exposure for cartilage excision. Hemostasis was easily maintained throughout the procedure with a handheld electrocautery. Four 10×20-mm rectangular portions of auricular cartilage were then measured and outlined on each ear, taking care to keep 0.5-cm strips of intact cartilage between each excised area. The cartilage rectangles were sharply excised while avoiding damage to the underlying dorsal auricular blood vessels. Three of the resulting cartilage defects were filled with the 10×20-mm polyethylene implants while a single silicone implant was placed into the fourth defect. The skin-perichondrium flap was then sutured back into its original position with 5-0 nylon sutures at the lateral ear border and between each implant site.

The rabbits were then divided into 3 groups of 3 animals, each with implants placed in both ears, for a total of 6 ears per group. Animals in group 1 underwent exposure of their implants on day 4 following implantation. Group 2 animals underwent exposure on day 7 after implantation while group 3 animals underwent exposure on day 21 following implantation. A single polyethylene implant in each ear served as a histological control and was not exposed. The remaining 2 polyethylene implants and the silicone implant were exposed on day 4, 7, or 21 following implantation by the removal of a 10-mm circular portion of skin directly over the center of the implant. Seven days after exposure, 1 exposed polyethylene implant in each ear received a full-thickness skin graft harvested from the nape of the neck. The donor site was closed primarily. The skin grafts were sutured to the exposure sites with interrupted 5-0 nylon sutures after light débridement of any eschar overlying the implant surface. All animals were fitted with protective collars after implantation to prevent manipulation of the operative sites. The wounds were then monitored closely for signs of infection, seroma, or hematoma formation. The status of each ear was documented with photographs throughout the course of the study.

At the conclusion of the study the animals were killed in accordance with animal care and research guidelines at the Beth Israel Medical Center, New York, NY. The ears were removed and stored in formalin. Histological preparations were made with full-thickness cross-sectional specimens from each implant site. Hematoxylin-eosin staining was performed for light microscopic analysis. All histological processing was performed at the Department of Pathology, The New York Eye and Ear Infirmary, New York City. All procedures were reviewed and approved by the Committee on Scientific Affairs and the Committee of Animal Care and Use at the Beth Israel Medical Center. The animals were treated in accordance with procedures outlined by the National Institutes of Health, Bethesda, Md.

(Medpor Ultrathin Sheets, Porex Surgical Inc, College Park, Ga) and hydroxyapatite have generated interest because of the observation of fibrous and bony tissue ingrowth within the implant material, which improves tissue tolerance. Hydroxyapatite is difficult to manipulate because of its rigidity and has limited applications in certain anatomical regions, such as the auricle with its complex 3-dimensional shape. Porous high-density polyethylene possesses thermoplastic properties that allow ease of contouring without disturbing the macromolecular structure of the implant. The fibrous incorporation of the implant by recipient tissue yields increased vascularity and resistance to bacterial infection as well as improved stability over time.

Several studies[2-5] report rapid fibrovascular and bony ingrowth in these polyethylene implants used to reconstruct craniofacial defects. The use of these polyethylene frameworks to reconstruct auricles in burn patients is described by Wellisz.[6] In that study, 2 implants became exposed because of sloughing of the overlying fascial flap and skin. One of the implants received a skin graft directly while the other was allowed to close via secondary intention. Both cases yielded acceptable reconstructions.

Investigations into the biocompatibility of an expanded polytetrafluoroethylene patch (Gore-Tex Soft Tissue Patch, Gore & Assoc Inc, Flagstaff, Ariz) using a rabbit model were conducted by Maas et al.[7] Portions of the expanded polytetrafluoroethylene material were placed in subcutaneous pockets overlying the dorsum of the nose. Specimens of the skin, implant, and nasal bone were analyzed at intervals from 3 weeks to 12 months using standard histological and electron microscopic techniques. The results showed a trend in increasing tissue stability over time with minimal inflammatory response. The surrounding fibrous capsule remained thin and there was little or no evidence of alteration in implant structure. The expanded polytetrafluoroethylene material is similar to polyethylene but is manufactured in flat sheets and lacks the ability to maintain precise rigid shapes, which the molding process imparts to the polyethylene.

Recent animal studies by Sclafani et al[8] examine the effects of exposure and skin grafting on polyethylene implants using a rat model. Polyethylene implants were placed subcutaneously and later exposed to simulate skin sloughing. The wounds were then covered with a skin graft or allowed to heal secondarily. The results showed excellent tissue tolerance of the polyethylene implants in the

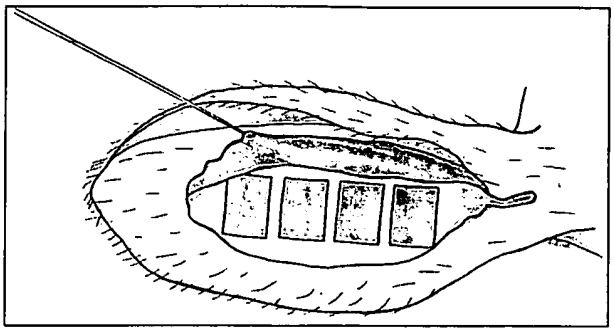

Figure 1. *Diagram of a rabbit ear showing placement of the skin-perichondrium flap and implant locations.*

Results of Implantation, Exposure, and Successful Skin Grafts for All Experimental Groups

Implant Type	Control	Exposed	Skin Grafts	Extruded
		Group 1		
Polyethylene	6	12	6	0
Silicone	2	4	0*	4
		Group 2		
Polyethylene	6	12	6	0
Silicone	2	4	0*	4
		Group 3		
Polyethylene	6	12	6	1
Silicone	2	4	0*	4

**In group 1, one attempted skin graft failed completely; in group 2, three attempted skin grafts failed completely; and in group 3, two attempted skin grafts failed completely.*

face of exposure and external contamination. Wound healing improved as the interval between implantation and exposure was lengthened from 2 to 14 days.

The current study was designed to more fully evaluate the nature of auricular wound healing in the setting of the exposed polyethylene implant material in a rabbit model. The implants were used to reconstruct surgically created defects in native auricular cartilage in the face of wound exposure with or without added skin graft coverage.

RESULTS

All animals survived the duration of the study and no implant sites became infected. A total of 54 of the polyethylene implants were placed with a single extrusion, while 12 of 18 silicone implants underwent extrusion (**Table**).

The polyethylene implants in group 1 (exposure on day 4) were all adherent to the surrounding tissues at the time of exposure, while the silicone implants remained mobile throughout the study. Seven days after exposure (day 11) these polyethylene implants were coated with a coagulum of blood, which bled when lightly abraded (**Figure 2**). Three of the 4 silicone implants extruded. Twenty days after exposure (day 24) all the exposed silicone implants had extruded with complete failure of the single attempted skin graft. Wounds with the exposed ungrafted polyethylene implants had undergone partial closure of the site. The exposed polyethylene implants

Figure 2. *Group 1 polyethylene implant exposure; note bleeding from implant surface (small arrow).*

were again covered with a coagulum of blood and bled when abraded. Seven of the polyethylene implants received skin grafts: 5 supported a 100% take of the graft while the remaining 2 supported a 50% take. The single silicone implant to have a skin graft placed demonstrated complete graft failure with subsequent extrusion of the implant.

All wound sites in group 2 (exposure on day 7) were well healed at both the polyethylene and silicone implant sites at the time of implant exposure. Seven days after exposure (day 14) 1 of the 4 silicone implants had extruded, while the other 3 remained fully exposed in the wounds. All 12 of the exposed polyethylene implants were covered with clotted blood and bled when abraded.

Three weeks after implant exposure (day 28) all the exposed silicone implants in group 2 had extruded and all 3 attempted skin grafts had failed. The 6 exposed polyethylene implants that did not receive skin grafts all showed complete wound healing and the polyethylene implants that received skin grafts all showed 100% graft survival.

The polyethylene implants in group 3 (exposure on day 21) were all noted to be surrounded by fibrous tissue that made them adherent to the overlying dermis. The silicone implants were encased in a dense layer of fibrous tissue that was not adherent to the implants. Seven days after implant exposure (day 28) 2 of the 4 silicone implants had extruded while the other 2 remained exposed in the wounds. Eleven of the 12 exposed polyethylene implants demonstrated more than 50% reepithelialization while the remaining implant showed minimal wound closure. The 6 polyethylene implants that underwent skin grafting were fully reexposed by sharp excision of the reepithelialized area over the original exposure site. All the implant sites bled when abraded.

Twenty-one days following exposure (day 42) all the exposed silicone implants had extruded and the 2 attempted skin grafts had failed completely in group 3. A single exposed, ungrafted polyethylene implant was noted to have sloughed 50% of the overlying skin coverage. Though it was partially extruded it remained adherent to the underlying deep wound surface within the carti-

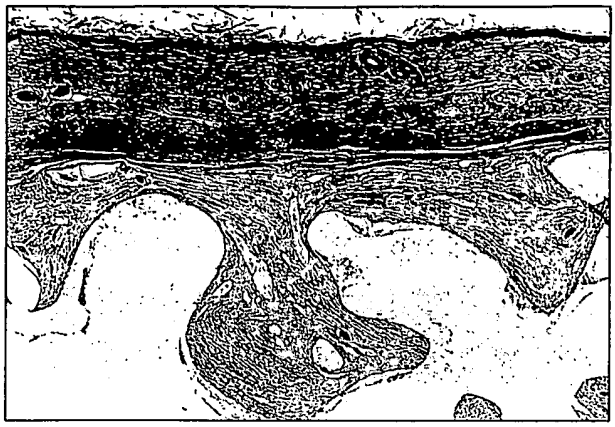

Figure 3. *Control polyethylene implant; note the surrounding fibrovascular tissue and the degree of tissue ingrowth within the substance of the implant (hematoxylin-eosin, original magnification ×4).*

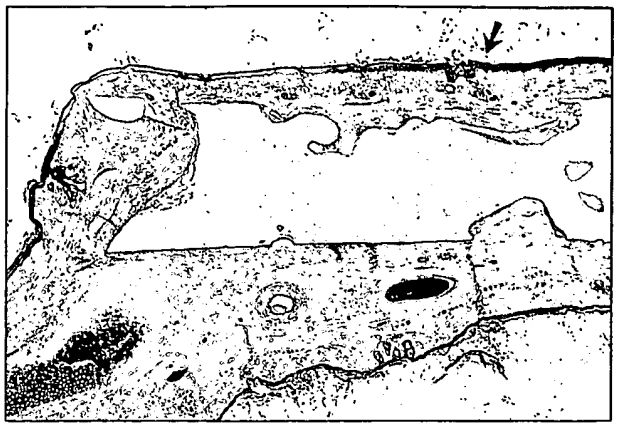

Figure 5. *Group 2 exposed polyethylene implant with full reepithelialization present 2 weeks following exposure. The arrow points to the exposure site (hematoxylin-eosin, original magnification ×2).*

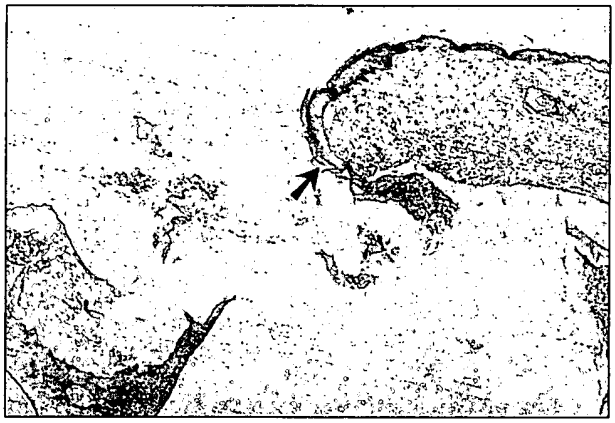

Figure 4. *Group 1 polyethylene implant exposure site; note the epithelial tissue advancing over the exposed surface (arrow) (hematoxylin-eosin, original magnification ×4).*

Figure 6. *Group 1 exposed polyethylene implant with a full-thickness skin graft in place over the exposure site (hematoxylin-eosin, original magnification ×4).*

lage defect. The remaining exposed, ungrafted polyethylene implants demonstrated complete reepithelialization over the exposure sites. All 6 of the exposed polyethylene implants that received skin grafts showed complete graft survival.

Findings of histological examinations of the unexposed polyethylene implants in all 3 groups demonstrated uniform fibrous tissue ingrowth by day 24. There was minimal inflammatory reaction present. The fibrovascular tissue surrounding the implants was noted to be only slightly thicker by day 42 (**Figure 3**).

The implants in group 1 (postexposure day 20, study day 24) were all incompletely reepithelialized and demonstrated a partial layer of necrotic material over the exposed implant surface. Epithelial migration was uniformly noted advancing from the periphery of the exposure sites (**Figure 4**).

The exposed implants in group 2 (postexposure day 21, study day 28) all demonstrated complete reepithelialization of the exposure sites (**Figure 5**). Evidence of fibrovascular tissue growth into the implant was present on all implant surfaces, including the exposed one. The fibrovascular tissue was noted to span the entire implant thickness in many areas. There was little evidence of inflammatory reaction around the implant margins or within the interior of the implants.

The implants in group 3 (postexposure day 21, study day 42) also showed complete reepithelialization over the exposed areas. The epithelium and subepithelial tissue layer was thicker than that seen in group 2. Numerous blood vessels were noted within the capsule surrounding each implant.

The polyethylene implants in group 1 supported skin grafts on their exposed surfaces (**Figure 6**). The grafts maintained their thickness during the study and fibrovascular tissue could be seen bridging the space between skin graft and implant surface. The implants in groups 2 and 3 also demonstrated preservation of graft thickness and maintenance of skin appendages with more extensive fibrovascular tissue ingrowth than seen in group 1 (**Figure 7**).

COMMENT

Alloplasts have been used for many years in facial reconstruction and augmentation with varying degrees of success. The ideal alloplastic material would show excellent host tissue tolerance, be easily manipulated to produce the required shape, show minimal recipient

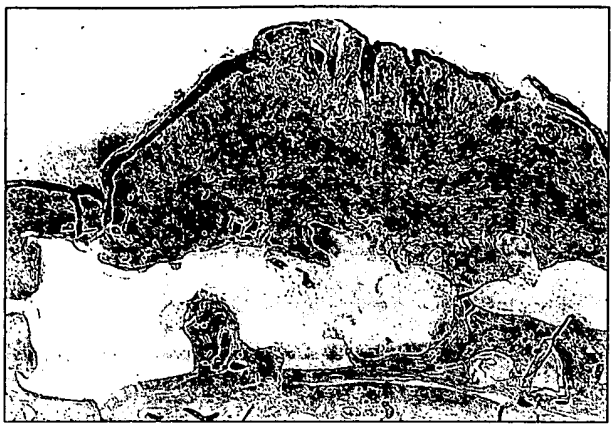

Figure 7. *Group 2 exposed polyethylene implant with a full-thickness skin graft in place over the exposure site; note preservation of skin appendages (hematoxylin-eosin, original magnification ×4).*

capsule formation, and demonstrate host tissue ingrowth, making it similar to native tissue. To date, the most significant drawback to the use of alloplasts has been the poor resistance to infection, with resultant implant extrusion. Results of work by Merritt et al[9] suggest that porous implants are more resistant to infection than nonporous implants if bacterial contamination happens after fibrous tissue ingrowth has occurred, but are at increased risk of extrusion if the bacteria are present prior to fibrous tissue ingrowth.

Solid silicone implants do not become integrated into recipient tissues and are thus prone to extrusion after infection or trauma. Omori et al[1] have reported frequent wound dehiscence when Dacron-covered silicone implants were used to reconstruct grades 1 and 2 microtias. They also noted a 9.5% rate of extrusion, occurring as long as 2 years after implantation. Porous polytef (Proplast, Vitek Inc, Houston, Tex) has been found to elicit a vigorous inflammatory response, resulting in degradation of the implant with resultant particle shedding and migration, despite the fact that it is a porous material with the potential for soft tissue ingrowth.[2,5,10,11] These drawbacks severely limit the use of this porous polytef in facial reconstruction. Polyamide mesh (Supramid, S. Jackson Inc, Alexandria, Va) allows soft tissue ingrowth but also causes a vigorous inflammatory response.[10]

Porous high-density polyethylene has been found to promote fibrous tissue ingrowth into its pores, which range in size from 100 to 250 μm. Tissue fluid circulates throughout the densely interconnected pores of the implant, which promotes rapid tissue ingrowth and vascularization.[12] The capsule formation is thin and flexible and causes a minimal inflammatory response. Shanbhag et al[13] implanted a small number of silicone and polyethylene disks into the auricular cartilage of baboons and found that 2 of 4 silicone implants extruded within 9 weeks of placement. The polyethylene implants became exposed but did not extrude in the same time interval. The exposures were preceded by eschar formation and subsequent skin sloughing. The exposures were thought to be caused by ischemic changes in the overlying skin, but the implants were retained because of fibrous tissue ingrowth and stabilization. Findings of histological examinations of their specimens revealed small blood vessels surrounding the polyethylene implants as well as ingrowth of collagen and blood vessels at the periphery of the implants. In contrast to the peripheral zone, the central region of each implant contained inflammatory cells with little collagen deposition.

Sclafani et al[8] report that polyethylene disks implanted under the dorsal skin of rats were completely invaded with fibrovascular tissue in 14 days. Partial exposure of the implants had minimal effect on this process. The capsule of fibrovascular tissue was found to remain thin and flexible with a minimal foreign body reaction, compared with the thick inflammatory capsule that was seen surrounding the solid silicone disks used for comparison.

The current study demonstrates that polyethylene implants used to reconstruct auricular cartilage defects undergo a similar rapid invasion by fibrovascular tissue. The unexposed polyethylene implants were uniformly invaded by granulation tissue, which traversed the full thickness of the implant. Minimal inflammatory reaction was noted when the implants were harvested anywhere from 24 to 42 days after implantation. The native cartilage adjacent to the implants did not show signs of inflammation or necrosis with either the unexposed or exposed polyethylene implants. The polyethylene implants were well tolerated in the setting of a full-thickness cartilage defect with coverage by a skin-perichondrium flap. These findings are supported by the fact that none of the 18 unexposed polyethylene implants extruded spontaneously. The polyethylene implants maintained a high degree of adhesion within the auricular implantation sites and behaved much like native auricular tissue in this experimental model.

It is encouraging that exposed polyethylene implants were well tolerated in reconstruction of the auricle. The implants in group 1 that were exposed early (day 4) did not extrude. The rate of wound closure and coverage by epithelial migration was slow and none of the 6 implants demonstrated total coverage 20 days after the exposures were performed. Group 1 implants were most remarkable in their ability to support skin grafts placed 7 days after exposure. The grafts all demonstrated a blood supply that originated both from the periphery of the wound and from the surface of the implant itself (Figure 6). The implants in groups 2 and 3, which were exposed 7 and 21 days, respectively, after implantation, all demonstrated full epithelial coverage at the end of the study. It is interesting to note that the single partially extruded polyethylene implant occurred in group 3, which had the longest interval between implantation and exposure. Improper handling of the implant and/or auricular tissue may be responsible for the extrusion in this case. Given this partial extrusion, it is encouraging to note the degree of fibrous tissue adhesion present between implant and recipient tissues, which might permit secondary skin grafting in the clinical setting. None of the experimental animals developed chondritis in this study, but given the severity of this form of infection it is doubtful that polyethylene implants or any other alloplast would be retained in the setting of severe cartilage necrosis. All the polyethylene implants in groups 2 and 3 that received skin grafts healed with total graft survival.

Silicone implants were uniformly extruded after exposure regardless of the time interval between implantation and exposure. All attempts at skin graft placement over exposed silicone implants resulted in graft failure. This finding supports the concept that the grafts were nourished by vascular ingrowth directly from the exposed polyethylene implant surface and not primarily from the peripheral skin edge and soft tissue, which were unable to support skin grafts placed on solid silicone implants.

The results of this study suggest that polyethylene implants tolerate auricular wound exposure far better than nonporous silicone implants. This is because of the specific porosity of the polyethylene implants, which promotes vigorous fibrovascular ingrowth. This ingrowth makes the implants far more stable when exposed and promotes better healing by either secondary intention or skin grafting. Similar porosity is also present in polytef implants, which might demonstrate similar behavior in this setting but lack the structural rigidity that polyethylene provides. Porous high-density polyethylene auricular framework implants may offer a reasonable addition to the current armamentarium of techniques available for use in this challenging area of reconstructive surgery.

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EXHIBIT D

Porous High-Density Polyethylene for Orbital Reconstruction

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Objective: To determine the safety and efficacy of using porous high-density polyethylene (PHDPE) in the repair of orbital defects.

Design: Retrospective case series.

Setting: Academic tertiary care trauma center.

Patients: One hundred seventy patients with orbital defects requiring surgical repair.

Intervention: Orbital defect repair with PHDPE.

Main Outcome Measure: Our review documents surgical results and complications associated with the use of PHDPE.

Results: There was a 6.4% complication rate associated with the use of PHDPE. The infection rate was 1.8%. The persistent orbital malposition rate was 3.5%. The extrusion rate was 0%.

Conclusions: This report represents the largest case series in the literature using PHDPE for orbital reconstructions. The use of PHDPE resulted in a low complication rate and excellent functional and cosmetic reconstructive results. Because of our success with the use of PHDPE, we have changed our clinical practice to minimize the use of autologous graft material, thereby eliminating donor site morbidity in cases involving orbital reconstruction.

Arch Otolaryngol Head Neck Surg. 2005;131:446-450

ORBITAL FRACTURES MAY result in globe malposition and restriction of ocular movement, causing diplopia and impairing vision. Reconstruction of orbital wall defects is required to maintain globe position and unrestricted ocular motility in cases involving large defects or entrapment of orbital tissue. Autograft materials have been shown to be a reliable method for repairing orbital defects. Autogenous implants, particularly cranial bone and nasal septal cartilage, have been advocated because of their resistance to the infections that can be caused by long-term exposure to organisms of the paranasal sinuses. However, harvesting autogenous grafts increases operative time and, depending on the graft location, is associated with the potential of serious donor site morbidity. Adapting these relatively flat and inflexible grafts to the complex contours of the orbit without compromising their integrity may also prove difficult.

Alloplastic materials also have been used to reconstruct orbital defects.[1] Alloplastic materials are easier to mold into the desired shape, but their use in orbital reconstruction has the potential for increased risk of infection. Implant migration may require implant removal. Of the many alloplasts that are available, we have increasingly used porous high-density polyethylene (PHDPE) (Medpor; Porex Surgical Inc, College Park, Ga) to repair orbital defects. Porous high-density polyethylene is a nonreactive material that allows vascular and soft tissue ingrowth, which is thought to enhance stabilization of the implant and promote resistance to infection. Our goals were to document and analyze any complications directly related to the use of PHDPE that required revision surgery and to establish guidelines for the use of this alloplastic material in orbital reconstruction.

Author Affiliations: Departments of Otolaryngology, University of Washington, Seattle (Drs Lee, Maronian, Most, and Whipple); Harborview Medical Center, University of Washington (Drs McCulloch and Stanley); and University of California at Davis, Sacramento (Dr Farwell).
Financial Disclosure: None.

METHODS

We performed a retrospective review (institutional review board No. 03-9315-E 01, Human Subjects, University of Washington, Seattle) of 170 cases in which PHDPE was used for the reconstruction of orbital defects at Harborview Medical Center, Seattle, from March

1998 to October 2003. All patients underwent an ophthalmologic examination before surgery, the extent of which depended on the patient's neurologic status. We examined the size, location, and cause of the defect; the preoperative signs and symptoms; the procedure performed; the type and number of PHDPE implants used, and the postoperative outcomes. Patients who did not undergo a follow-up examination at least 6 weeks after their surgery were not included in the study.

RESULTS

Porous high-density polyethylene was placed into 190 orbits in 170 patients. One hundred sixty-five patients (97.1%) were treated for traumatic injuries, 12 (7.3%) of which were delayed reconstructions (>6 weeks from time of injury). The remaining 5 patients (2.9%) underwent tumor extirpation that resulted in a bony orbital defect. Of the 165 patients with traumatic injuries, 80 (48.5%) had an orbitozygomaticomaxillary fracture or a Le Fort II/III fracture variant. Fifty patients (30.5%) had an isolated orbital floor injury, while the remaining 35 patients (21.2%) had panfacial or bilateral fractures. Fifty-six (33.9%) of the patients with traumatic injuries presented with acute or delayed enophthalmos, 84 (50.9%) presented with restriction of ocular movement, and 30 (18.2%) presented with both enophthalmos and restriction of ocular movement. Twenty-two patients (13.3%) had normal results on their ocular examination but had evidence of involvement of more than 50% of the orbital floor on computed tomographic scans. Twenty-eight patients (17%) could not be fully examined because their neurologic status precluded an accurate assessment of ocular motility (forced duction testing was not performed). All 5 patients with tumors exhibited signs of proptosis and limited ocular motility.

One hundred forty defects (73.7%) involved the inferior orbital floor, 35 (18.4%) the medial orbital wall, 14 (7.4%) the lateral orbital wall, and 1 (0.5%) the superior orbital wall. In 35 patients (20.5%), PHDPE was used to repair orbital defects that encompassed more than 1 orbital wall. The majority of the inferior, medial, and lateral orbital wall defects were approached through a transconjunctival incision. Endoscopic-assisted repair of inferior orbital floor defects through a Caldwell-Luc approach was successful in 20 (87.0%) of 23 patients (**Figure 1** and **Figure 2**). A transconjunctival approach was successfully used for placement of the implant in the cases in which the endoscopic attempt at repair failed. Medial orbital wall fractures that were inaccessible through a transconjunctival approach were repaired via multiple other approaches, including 1 transcaruncular approach and 2 Lynch incisions, while the remaining orbital defects were approached through a coronal incision for panfacial trauma or existing lacerations. The superior orbital roof implant was placed via a Lynch incision.

All patients had been given preoperative steroids (dexamethasone, 10 mg) and a broad-spectrum antibiotic. In all, 205 implants were used to repair 190 orbital defects. None of the implants were soaked in antibiotic solution before insertion. One hundred forty implants were single-sheet nonchanneled PHDPE: 90 (39.8%) were 0.4 mm in thickness, 50 (24.8%) were 0.85 mm in thickness, and

Figure 1. Endoscopic approach depicting isolation of orbital defect before placement of porous high-density polyethylene (Medpor; Porex Surgical Inc, College Park, Ga) implant.

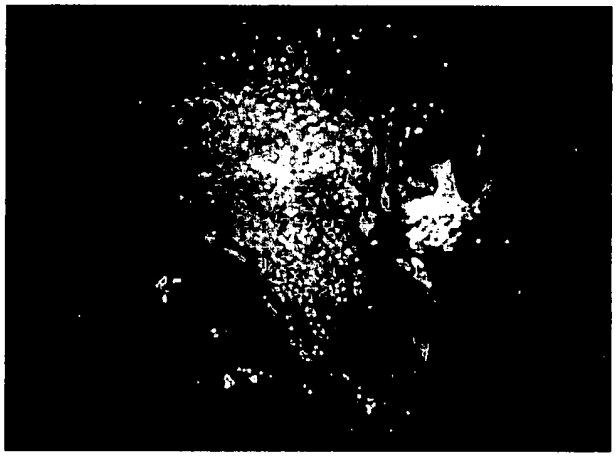

Figure 2. Successful placement of porous high-density polyethylene (Medpor; Porex Surgical Inc, College Park, Ga) implant to repair inferior orbital defect via endoscopic approach.

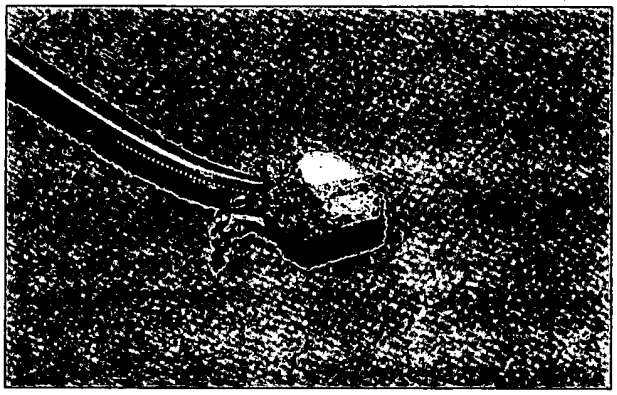

Figure 3. A 1.0-mm titanium miniplate in single-channel porous high-density polyethylene (Medpor; Porex Surgical Inc, College Park, Ga) implant before implantation.

14 (6.8%) were 1.0 mm in thickness. Thirty-nine implants (24.0%) were single-channel PHDPE implants (0.85 mm in thickness) (**Figure 3** and **Figure 4**), and 12 (9.0%) were multichannel PHDPE implants (2.3 mm in thickness). The majority of the surgeons did not use any form of fixation for the nonchanneled implants or close

Figure 4. Single-channel porous high-density polyethylene (Medpor; Porex Surgical Inc, College Park, Ga) implant cantilevered off left inferior orbital rim to repair inferior orbital defect viewed superiorly.

the periosteum of the orbital rim after placement of the implant. One surgeon placed a single screw anteriorly to hold the implant when a channeled implant was not used and closed the periosteum over the implant when possible. One-millimeter titanium plates (Synthes, Paoli, Pa) were used to cantilever the channeled implants from the orbital rim.

The average length of follow-up for all patients was 7.4 months. Complications were noted in 11 (6.4%) of the 170 patients. One case of blindness resulted from a retrobulbar hematoma due to uncontrolled hypertension, despite an emergent canthotomy, removal of implant, and evacuation of the hematoma. The displacement of 2 implants (both 0.4 mm in thickness, unfixed, and placed through a modified transconjunctival approach) resulted in obstruction of the maxillary ostia, causing maxillary sinusitis. The implants were removed, with no further sequelae. Interestingly, neither of the patients involved had any evidence of enophthalmos. There was 1 case of an infected single-channel implant (with a 1.0-mm titanium miniplate placed through a standard transconjunctival approach), with an orbital abscess requiring removal and drainage. There were 7 cases of persistent enophthalmos after primary repair that required revision. Three of our patients with persistent enophthalmos were found to have slipped implants (2 single-channel and 1 nonchanneled) at the time of reoperation; replacing these implants in their anatomical position corrected the enophthalmos. One of the 3 patients experienced a second trauma to the surgical site a few weeks after his primary repair. The rest of our cases of enophthalmos were thought to be attributable to inadequate re-creation of the posterior orbital volume, cicatricial scarring, or orbital fat atrophy due to trauma. These cases of enophthalmos were corrected by medial and lateral augmentation of the orbital walls with PHDPE or by re-creation of the posterior convexity of the orbital floor with stacked sheets of PHDPE. The rest of our patients had resolution of any enophthalmos and/or ocular movement restriction that had been present before surgery. There were 3 cases of ectropion and 1 case of entropion, 2 of which required surgical revision. The single case of entropion occurred after a formal lateral canthotomy incision, while the other cases of eyelid malposition occurred after the modified transconjunctival approach. All of these cases involved nonchanneled PHDPE. However, all of these cases had comminuted orbital rim defects that were repaired with titanium miniplates.

COMMENT

Medpor is formed by sintering small particles of high-density polyethylene to create strong, firm material that can be molded by hot water. It maintains its shape because it does not disrupt the overall macromolecular structure of the implant. Pore sizes range from 100 to 250 μm (50% are larger than 150 μm). This porous material allows fibrovascular ingrowth into the implant, preventing capsule formation and promoting stabilization of the implant.[2] Foreign bodies have been shown to reduce the number of bacteria required to produce infection by a factor of 10^4 to 10^6.[3] Recent studies have shown that because of the increased fibrovascularization, PHDPE is more resistant to infection than another porous allograft material, expanded polytetrafluoroethylene.[4] Immediate infections are thought to occur more often with porous alloplastic material because of the increased surface area associated with the porous material. However, the increase in surface area makes the implant more resistant to late infections because fibrovascularization of the implant allows increased immune response mediators at the site.[5] This fibrovascularization is evidenced by the ability of computed tomography and magnetic resonance imaging to show enhancement of PHDPE radiographically.[6] Also, experimentally exposed porous polyethylene that has been invaded by fibrovascular tissue has shown the ability to support skin grafts and promote healing by secondary intention in rats.[7] The fibrovascularization not only protects the implant from infection but also prevents its migration.[8] Theoretically, speeding up the time for fibrovascularization may enhance the early stability of the implant as well as its resistance to infection. Autologous blood clot, epidermal growth factor, and basic fibroblast growth factor have been found to speed fibroblast incorporation into the PHDPE implants after 2 weeks of implantation in rats.[9-11]

In our experience, PHDPE has been used to repair orbital defects successfully, with a very low complication rate, and most of the complications that did occur were not related to the implant itself. There was 1 case of orbital abscess associated with the implant, but a titanium plate or devitalized tissue may also have been a source of infection. Considering that the majority of our implants were placed in the setting of exposed sinus contents, the rate of infection was remarkably low. We do not soak our implants in antibiotic solution, as some authors recommend. Maxillary sinusitis is common after midface fractures,[12] but when an implant has been placed, infected plates and/or slipped implants should be considered as possible sources of nonresolving sinusitis. We can conclude that the use of PHDPE results in a very low rate of infection and that presoaking the implants in an antibiotic solution is unnecessary.

One potential key to the use of PHDPE is to ensure fixation of the implant to avoid displacement, which may result in obstruction of the maxillary sinus ostia, globe malposition, restriction of gaze, or direct pressure on the optic nerve from posterior displacement. We have transitioned our practice somewhat, using an increasing number of the single-channel implants fixated to the orbital rim to ensure stability of the implant. Placing cantilevered implants in the presence of an orbital rim fracture requires planning to prevent the cantilevered plate from crossing the orbital rim fixation plate if at all possible. Overlapping the orbital rim plate with the cantilevered plate can result in the plates being more readily palpable and may cause destabilization of the microplate that is attached to the PHDPE implant. Placing a screw anteriorly to fixate the implant is a useful technique, but it is not always possible, particularly if the rim is comminuted. Likewise, closing the periosteum over the rim may help secure the implant but also is not possible in every case. Multichannel implants are used when more than 1 orbital wall is re-created, when 2-plate fixation is needed for implant stability, or when a very thick piece of porous polyethylene is required. The use of multichannel implants in this manner has been reported to be successful and has not been associated with an increased infection or complication rate.[13,14] We, too, have not found an increased complication rate associated with multichannel implants. We have had excellent results without fixation of the implant, presumably because of fibrovascularization of the implant. We should note that none of our patients who had a successful endoscopic repair of an orbital floor defect have experienced postoperative complications due to a lack of fixation of the implant. Two of our patients with persistent enophthalmos had displaced single-channel implants. Despite fixation of the implant to the anterior orbital rim, at least 1 adequate posterior, medial, or lateral ledge is still required to help support the orbital contents. It is likely that the implants were not adequately positioned during the initial operation.

There have been other retrospective reviews that have examined the use of PHDPE for orbital defect repair (**Table**).[13,15-24] Porous high-density polyethylene has an extremely reliable track record in terms of infection. Our study does have some limitations. We did not formally measure enophthalmos with an exophthalmometer at the time of surgery. Correlating preoperative signs and symptoms with postsurgical outcomes is difficult in patients with traumatic injuries because most of them undergo surgery within 2 weeks of their acute injury. Therefore, continued edema limited our ability to determine the exact degree of enophthalmos and restriction of eye movement. Also, the follow-up period for most of our patients was relatively short. For complete assessment of the accuracy of re-creating orbital volume and prevention of enophthalmos, as well as resistance to implant extrusion and infection, longer-term follow-up is required. We can state that when the acute swelling due to the procedure has subsided, our results have been excellent, at least in the short term.

In general, as a matter of personal preference we do not use PHDPE to re-create the medial orbital walls in cases of panfacial trauma involving the skull base with exposed dura. Despite repair of the skull base defect with a pericranial flap, the proximity of the implant to the dura and paranasal sinuses concerns us. In such cases, a coronal flap is almost always indicated and harvesting cranial bone graft is easily performed. We also prefer to use cranial bone graft for reconstruction of our significant temporal and orbital defects after sphenoid wing or orbital tumor resections with exposed dura or brain.

In conclusion, porous high-density polyethylene is a safe and effective tool for use in craniomaxillofacial reconstruction. Overall, it is an excellent alternative to autogenous grafts, and its use results in decreased operative time and morbidity. In our series, the infection rate was very low and there were no problems with extrusion.

Table. Review of Porous High-Density Polyethylene for Orbital Reconstruction

Source	No. of Patients	% (No./Total No.) Infection Rate	% (No./Total No.) Persistent Globe Malposition
Chen and Chen[20]	3	0	0
Choi et al[19]	32	3.1 (1/32)	3.1 (1/32)
Folkestad and Granstrom[23]	44	0	19.0
Goldberg et al[24]	4	0	0
Hwang and Kita[22]	6	0	0
Ng et al[13]	30	3.3 (1/30)	3.3 (1/30)
Romano et al[18]	140	0.7 (1/140)	1.4 (2/140)
Rubin et al[17]	37	2.7 (1/37)	2.7 (1/37)
Villarreal et al[16]	32	12.5 (4/32)	37.5 (9/24)
Wellisz et al[21]	15	0	0
Yaremchuk[8]	145	0	0
Present study	170	1.8 (3/170)	3.5 (6/170)

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Previous Presentation: This study was presented at the AO ASIF (Association for Internal Fixation) Advanced Craniomaxillofacial Trauma Course; February 8, 2004; Sun Valley, Idaho.

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